IDENTIFYING COGNITIVE AND BEHAVIORAL ENDOPHENOTYPES IN FAMILIES WITH AUTISM SPECTRUM DISORDERS

by

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ABSTRACT

Individuals with autism spectrum disorders (ASDs) demonstrate a wide variety of clinical presentations. Although the etiology is unknown, it is likely that ASDs result from a complex interaction of genetic and environmental factors. It may also be the case that there are multiple types of ASD, each with their own unique etiology and developmental trajectory. It has been difficult to identify homogeneous groups of individuals with ASD that in turn makes it difficult to discover any etiology. Neurocognitive characteristics of ASD may be a helpful way to find ASD subtypes. However, consistent neurocognitive patterns in ASD have not emerged. One potential method for studying genetic etiology is to examine nonautistic family members. Certain characteristics of ASD have been shown to occur in other family members at a subclinical level. These are known as endophenotypes or intermediate traits that may be genetically related to ASD. If subtypes of ASD can be identified based on neurocognitive profiles, those same profiles may also exist in some family members as endophenotypes.

The present study aimed to examine the cognitive and behavioral profiles in families with ASDs. A cluster analysis utilizing constructs of IQ, language, social ability behavior, and adaptive behavior was performed on the affected family members. Similar methods and constructs were applied to unaffected family member data, and results were compared. Four clusters emerged in the affected

individuals and two in the unaffected individuals. The affected clusters demonstrated uneven profiles of IQ and adaptive ability; however, social ability did not appear to impact cluster membership, suggesting a dimensional versus severity gradient approach to classifying ASDs. The unaffected clusters also demonstrated uneven profiles differentiating themselves mostly on social ability. One cluster in the unaffected group appeared to have a similar profile to the most high-functioning affected cluster, suggesting that it may represent a broader autism phenotype with subclinical levels of ASD-related traits. These findings suggest that subtypes of ASD may exist and may be best identified using a dimensional approach that considers constructs outside the diagnostic criteria. In addition, unaffected family members may demonstrate similar profiles but at subclinical levels.

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INTRODUCTION

This thesis examined the cognitive and behavioral profiles in families with autism spectrum disorders (ASDs) as a way to identify distinct subtypes that might have their own genetic etiology. To lay the background, several areas are discussed: (a) the heterogeneity of ASDs and the current lack of distinct diagnostic subtypes, (b) neurocognitive profiles in ASDs, (c) genetic research on ASDs, and (d) possible endophenotypes related to neurocognitive profiles.

Heterogeneity of Autism Spectrum Disorders

The central features of autism were originally described by Kanner (1943). Autism was once thought to be a rare condition, and the early diagnostic criteria generally described severely impaired individuals. However, as the understanding of autism has increased, it is clear that there is a wide range of clinical presentations. Some individuals can be severely mentally retarded and noncommunicative, whereas others are intellectually gifted and excessively verbose.

Diagnostic criteria for autism have broadened to represent the wider range of clinical presentations. The criteria for autistic disorder have become less restrictive and now describe milder cases of autism. In addition, Asperger disorder, a form of mild autism, was included as a new diagnostic category.

The current *Diagnostic Manual of Mental Disorders* (DSM-IV-TR; American Psychiatric Association, 2000) classifies all ASDs under the category of pervasive developmental disorders. There are five types of pervasive developmental disorders, each of which is discussed in more detail below. All pervasive developmental disorders are associated with deficits in reciprocal social interaction, deficits in verbal and nonverbal communication, and a pattern of stereotyped behaviors and unusual interests. These three areas have become known as the "triad of impairments" associated with pervasive developmental disorders.

The five DSM-IV-TR (American Psychiatric Association, 2000) disorders classified under the pervasive developmental disorders category are (a) autistic disorder, (b) Asperger disorder, (c) Rett syndrome, (d) childhood disintegrative disorder, and (e) pervasive developmental disorders-not otherwise specified. As is discussed below, childhood disintegrative disorder and Rett syndrome appear to have distinct etiologies and courses that may be separate from the other disorders. The remaining three (autistic disorder, Asperger disorder, and pervasive developmental disorders-not otherwise specified) have come to be called ASDs. These three diagnostic categories are similar to each other, and it is not yet clear whether they identify distinct groups of individuals.

The DSM-defined criteria for autistic disorder include impairments in three major areas: (a) social interaction, (b) communication, and (c) restricted repetitive and stereotyped patterns of behaviors, interests, and activities. The individual must demonstrate at least six symptoms across the three categories with at least two

symptoms in the social interaction domain. In addition, delays or abnormal functioning in social interaction, language, or play skills must be present before age 3. Finally, to obtain a diagnosis for autistic disorder, Rett syndrome and childhood disintegrative disorder (described below) must be ruled out.

The developmental course of autistic disorder is not well understood. Some individuals with autistic disorder demonstrate apparently normal development for the first 1 to 2 years of life, but others (approximately 20% to 40%) have a developmental regression during infancy or the toddler years (Hoshino et al., 1987; Kurita, 1985). Poorer mental development, communication skills, and poorer outcome are associated with regression in autism (Rogers & DiLalla, 1990). Approximately 75% of individuals with autistic disorder are verbal and have cognitive abilities within the nonimpaired range. This group is considered "high functioning" even though their social and communication impairments can be significant.

The diagnostic criteria for Asperger disorder are similar to autistic disorder. Individuals with Asperger disorder must show at least two examples of impairments in social interaction as well as at least one example of restricted, repetitive, or stereotyped behavior. Asperger disorder requires that no clinically significant delays in language (e.g., single words used by 2 years and communicative phrases used by 3 years) or cognitive development are evident; thus, by definition, individuals with Asperger disorder are high functioning. DSM-IV-TR criteria specify that a diagnosis of childhood disintegrative disorder, Rett

syndrome, and autistic disorder must first be ruled out before Asperger disorder can be diagnosed (American Psychiatric Association, 2000).

Rett syndrome shares some behavioral features with autistic disorder; however, the course and onset of the development of the disorder are distinct from other pervasive developmental disorders. First, the disorder occurs exclusively in females. Following a period of apparent healthy infant development, a number of characteristics emerge: (a) rapid deceleration of head growth between the ages of 5 and 48 months of age, (b) loss of purposeful hand movements between 5 and 30 months of age, (c) loss of social engagement, (d) appearance of gait and truncal apraxia/ataxia, and (e) severely impaired expressive and receptive language development with profound psychomotor retardation. During the preschool years, Rett syndrome is behaviorally similar to autism in the areas of social interaction and restricted and stereotyped behaviors (Tsai, 1992b). However, these "autistic-like" traits tend to diminish over time (Hagberg, 1989; Hagberg, Aicardi, Dias, & Ramos, 1983) and more typical social interaction develops later in life (Gillberg, 1987). A mutation in the gene encoding methyl-CpG-binding protein 2 (MECP2) was detected in Rett syndrome in 1999 (Amir et al., 1999). Since this discovery, the course of Rett syndrome has been found to relate to abnormal synaptogenesis at different developmental stages (Segawa & Nomura, 2005).

Like Rett syndrome, childhood disintegrative disorder shares some characteristics with other pervasive developmental disorders but appears to be diagnostically distinct. To receive a diagnosis of childhood disintegrative disorder,

an individual must demonstrate apparently normal development for at least the first 2 years of life, with a subsequent profound and irreversible loss of acquired skills in a number of areas (e.g., language, social skills, play, and motor abilities; American Psychiatric Association, 1994; Volkmar, 1992). The speech loss associated with childhood disintegrative disorder has been more thoroughly examined than that observed in autism or even Rett syndrome (Kurita, Koyama, Setoya, Shimizu, & Osada, 2004). In addition, the individual must demonstrate abnormalities in two of the three areas of pervasive developmental disorders impairment. Research has demonstrated that childhood disintegrative disorder is diagnostically distinct from autism based on past DSM criteria (Mouridsen, Rich, & Isager, 1998). Individuals diagnosed with childhood disintegrative disorder early in life may demonstrate improvements in cognitive or language abilities. However, the majority continues to meet criteria for mental retardation, seizure disorder, and pervasive developmental disorders (Burd, Ivey, Barth, & Kerbeshian, 1998).

Finally, pervasive developmental disorders-not otherwise specified is used to describe individuals who do not meet criteria for another pervasive developmental disorder but who demonstrate impairment in at least two of the three areas of pervasive developmental disorders impairment. Pervasive developmental disorders-not otherwise specified is often used to describe mildly affected individuals as well as individuals whose presentation is for some reason atypical. In general, individuals with pervasive developmental disorders-not otherwise specified demonstrate fewer symptoms than do those with autistic

disorder (Buitelaar, Van der Gaag, Klin, & Volkmar, 1999; Waterhouse, Morris, & Allen, 1996), but the group is heterogeneous.

Difficulty Differentiating Between Autism Spectrum Disorders Categories

Childhood disintegrative disorder and Rett syndrome are easily differentiated from other pervasive developmental disorders because of their cardinal symptoms and distinct trajectories of development. Differentiating between autistic disorder, Asperger disorder, and pervasive developmental disorders-not otherwise specified has been more difficult.

Both Asperger disorder and autistic disorder demonstrate overlap in the areas of social interaction and restricted repetitive and stereotyped behavior. While communication impairments are not included in Asperger disorder criteria, neither are they specified as exclusionary; thus, individuals with Asperger disorder may or may not show communication impairments. Likewise, while individuals with Asperger disorder must have not had an early language delay, individuals with autistic disorder may or may not have had a language delay. Thus, in practice, individuals with Asperger disorder and autistic disorder can look similar. Indeed, many who meet DSM-IV-TR criteria for Asperger disorder also meet criteria for autistic disorder (American Psychiatric Association, 2000; Eisenmajer et al., 1996; Miller & Ozonoff, 1997; Szatmari, Archer, Fisman, Streiner, & Wilson, 1995). In fact, one study demonstrated that individuals with a diagnosis of autistic disorder in preschool, with no language delay, followed a similar developmental trajectory

measured by IQ, social skills, and adaptive skills as those diagnosed with Asperger disorder in preschool (Szatmari, Bryson, Boyle, Streiner, & Duku, 2003). Furthermore, research has not demonstrated that Asperger disorder and autistic disorder differ in terms of neuroanatomical findings (Lotspeich et al., 2004), neuropsychological profiles (Barnhill, Hagiwara, Myles, & Simpson, 2000; Jansiewicz et al., 2006; Manjiviona & Prior, 1999; Miller & Ozonoff, 2000; South, Ozonoff, & McMahon, 2005; Spek, Scholte, & van Berckelaer-Onnes, 2008; Verte, Geurts, Roeyers, Oosterlaan, & Sergeant, 2006), outcome (Bennett et al., 2008; Howlin, 2003), or treatment response (Szatmari, 2000). However, no studies have yet examined response to treatment for autistic disorder and Asperger disorder and compared them.

Pervasive developmental disorders-not otherwise specified is based on the same three areas of impairment and is diagnosed when criteria for another pervasive developmental disorder are not met. Thus, individuals with pervasive developmental disorders-not otherwise specified are qualitatively similar to those with autistic disorder or Asperger disorder, but they may have a smaller number of characteristics or some other atypical aspect to their presentation (e.g., a late age of onset and a comorbid medical condition that affects the pervasive developmental disorder symptom presentation).

To summarize, the current diagnostic system has responded to an understanding of the wide range of clinical presentations of ASDs. However, aside from Rett syndrome and childhood disintegrative disorder, the current diagnostic

categories do not yield distinct groups of homogeneous individuals. It may be important to study factors not currently captured by the diagnostic criteria in order to identify distinct subtypes of autism.

Neurocognitive Profiles of Autism Spectrum Disorders

Cognitive development is one potentially important factor that is not captured by current diagnostic criteria. The cognitive development of individuals with autism can vary widely and can include a history of mental retardation, average intellectual functioning, superior IQ scores, developmental regression in some (but not all) individuals, widely discrepant IQ domain scores in either direction (verbal or nonverbal skills), and significant gains in IQ scores with early intervention. Thus, studying neurocognitive profiles of individuals with ASD may help uncover subtypes that have different patterns of cognitive development or ability.

Intellectual Profiles in Autism Spectrum Disorders

Most, but not all, of the children first described by Kanner (1943) had some degree of mental retardation. However, the group Asperger (1944) described demonstrated generally "normal" intelligence. Until recent years, it was believed that up to 75% of individuals with autism might also have comorbid mental retardation (Ritvo, Ritvo, Freeman, & Mason-Brothers, 1994; Ritvo & Ariella Ritvo, 2006). However, it is now understood that the majority of individuals diagnosed with autism have IQs that are within the normal range (i.e., full scale IQ

[FSIQ] > 70; Kanner & Eisenberg, 1956; Klin, Volkmar, Sparrow, Cicchetti, & Rourke, 1995; Tsai, 1992a). These high-functioning individuals can meet diagnostic criteria for either autistic disorder or Asperger disorder, and they are generally undistinguishable from each other as adults even though some may have had more severe delays when younger.

A substantial amount of research has supported the idea that individuals with autism often have significant discrepancies in their intellectual profiles, showing superior ability in one area but impaired skills in other domains. Initially, it was once thought that a particular Wechsler IQ profile (verbal IQ [VIQ] < performance IQ [PIQ] + high block design) might be universal in autism; however, empirical studies have not supported this thinking (Siegel, Minshew, & Goldstein, 1996). Intelligence profiles were used to distinguish among possible ASD categories. Klin et al. (1995) compared the IQ profiles of individuals with Asperger disorder with those with autistic disorder. This study suggested that a VIQ>PIQ profile might be universal in autistic disorder and could be used as a potential way to distinguish between autistic disorder and Asperger disorder. In this study, individuals with Asperger disorder demonstrated higher VIQ compared with PIQ. However, other studies comparing Asperger disorder and autistic disorder have not found this pattern (Manjiviona & Prior, 1999; Miller & Ozonoff, 2000; Ozonoff, South, & Miller, 2000). These mixed results are likely due to the difficulty distinguishing between Asperger disorder and autistic disorder with the current diagnostic criteria. Thus, discrepant IQ profiles are common in ASDs and

may be related to subtypes that are not captured with the current diagnostic criteria.

It has been suggested that examining age, development, or symptom severity as factors influencing intellectual profiles may help yield more informative profiles. One approach to determining more accurate profiles has been to examine the IQ profiles of high- and low-functioning individuals at different ages. In discriminating between high- versus low-functioning individuals with autism, Lincoln, Courchesne, Allen, Hansen, and Ene (1998) found that in higher-functioning individuals the difference between VIQ and PIQ decreased with age and was associated with improvements in language functioning. Others have suggested that the discrepancies may decrease as overall intellectual ability increases (Rumsey, 1992; Siegel et al., 1996). A pattern of declining PIQ and improving VIQ has also been noted (Mawhood, Howlin, & Rutter, 2000). Lockyer and Rutter (1969) reported no change in cognitive abilities over time in ASDs; however, this finding has not been replicated. Although the above studies demonstrated that IQ profiles change over time, no consistent pattern was identified even when discriminating between high- and low-functioning individuals.

Joseph, Tager-Flusberg, and Lord (2002) attempted to determine whether symptom severity, age, and IQ yielded subtypes. In this study, discrepancies between verbal and nonverbal abilities occurred 56% of the time in younger children (age 5) and 62% of the time in older children (age 8). In the younger group, discrepancies were commonly found in favor of nonverbal abilities, whereas

verbal and nonverbal abilities were found to be equally discrepant in the older group. In the older group, it was also found that greater social impairment was associated with PIQ > VIQ. Although more research needs to be conducted to determine the role of symptom severity in IQ profiles, it is likely that in combination with age it may yield more accurate cognitive and social profiles in ASDs.

Language Profiles

Individuals with ASD vary widely in their language abilities, with some demonstrating no verbal language and others who are excessively verbose. Even in fluent individuals, however, difficulties with phonological processing, vocabulary, higher-order syntax, and semantics have been found (Lord & Paul, 1997; Rapin, 1996; Tager-Flusberg & Joseph, 2003). Subtypes have been examined in ASDs based on language ability. Tager-Flusberg and Joseph proposed a subtype of ASD that shares characteristics with individuals with specific language impairment. In addition, abnormal asymmetry of language regions in ASDs has been reported (Herbert et al., 2002). Although language has been extensively studied in ASD, as it is considered a core feature of the disorder, few studies have examined the developmental profiles of language in ASDs. The ability to acquire verbal language or other aspects of language may relate to ASD subtypes.

Sex

Differences in brain structure and development for typically developing children have been noted for sex (De Bellis et al., 2001; Giedd et al., 1999; Thompson et al., 2000). Previous research has also demonstrated that cognitive abilities, particularly visuo-spatial abilities, differ by sex (Hampson, 1995; Kimura, 1992). This finding implies that in healthy developing children there may be discrepancies in cognitive abilities.

In ASD, it has been found that females tend to be more cognitively impaired than males, despite the overall female-to-male ratio of ASD (Fombonne, 2003). However, in higher-functioning individuals, males appear to be more socially impaired early in development compared with females (McLennan, Lord, & Schopler, 1993). In a study of toddlers with ASD, girls achieved higher visual reception scores than boys when language ability was controlled for and boys attained higher language and motor scores and higher social-competence ratings than girls, particularly when controlling for visual reception (Carter et al., 2007). Thus, sex is an important but not well-studied variable to consider in ASDs, as differences between males and females may exist and follow different developmental pathways.

Genetics of Autism Spectrum Disorders

One result of identifying subtypes of ASD is to inform genetic studies of etiology. More than 89 genes have been implicated in autism (Wassink, Brzustowicz, Bartlett, & Szatmari, 2004); in fact, some researchers have suggested

the involvement of at least two and perhaps many interacting genes (Pickles et al., 1995; Risch et al., 1999). Difficulties in identifying clear genetic causes may be due to the heterogeneity of ASDs. By identifying more homogeneous groups of ASDs, the study of genetic influences may be more successful.

Research on the genetics of autism is relatively recent. In 1995, one of the first studies conducted using the family history method in individuals with pervasive developmental disorders found that their relatives had no more cognitive or psychiatric impairments than control families (Szatmari, Jones et al., 1995). However, they demonstrated more cases of pervasive developmental disorders in the extended families than in the control families, usually through the maternal line. Further studies revealed that families containing one child diagnosed with an ASD face a recurrence risk of approximately 15 to 30 times the risk of the general population (Bailey et al., 1998; Chakrabarti & Fombonne, 2001; Fombonne, 1999; Smalley & Collins, 1996; Szatmari, Jones, Zwaigenbaum, & MacLean, 1998). Twin studies indicated that concordance rates of ASDs in twins range from negligible concordance in dizygotic twins to between 36% and 91% concordance in monozygotic twins (Bailey et al., 1995; Folstein & Rutter, 1977; Steffenburg et al., 1989), suggesting a heritability estimate of between 70% and 90% (Bailey et al., 1995). Since monozygotic twins share 100% of their genes, a less-than-100%-concordance rate among monozygotic twins is likely due to environmental differences.

The search for genes relevant to ASDs is helped by studies of endophenotypes: intermediate characteristics in nonautistic family members that might be genetically related to ASDs. Several studies have searched for potential endophenotypes. Controlling for factors such as mental retardation, Boutin et al. (1997) suggested that females with autism have higher family histories of cognitive disabilities. Folstein et al. (1999) found that parents of children with autism, who themselves had a history of language difficulties as children, scored lower on tests of verbal ability compared with parents of children with Down syndrome. Two studies revealed a locus on chromosome 17 for families in which autism was present in males only (Cantor et al., 2005; Stone et al., 2004), suggesting potentially different genetic mechanisms for males and females. In addition, Coon et al. (2005) demonstrated that a potential subtype might exist for those with the brain-expressed tryptophan hydroxylase gene (TPH2) and higher scores on the Autism Diagnostic Interview-Revised domain describing repetitive and stereotyped behaviors. Thus, factors such as gender, cognitive and language abilities, and biological markers may relate to specific subtypes of autism, possibly with their own genetic etiology.

Neurocognitive Endophenotypes of Autism Spectrum Disorders

Early studies have demonstrated that relatives of individuals with autism also present traits related to autism with varying degrees of severity (Bailey et al., 1995; Bailey et al., 1998; Folstein & Rutter, 1977; Piven & Palmer, 1997; Piven,

Palmer, Jacobi, Childress, & Arndt, 1997; Piven, Palmer, Landa et al., 1997; Szatmari, Jones et al., 1995; Szatmari et al., 1998). The broader autism phenotype (BAP) describes the subclinical forms of ASD-related traits sometimes seen in family members and may be an endophenotype of ASDs. The BAP includes general language impairments, social difficulties, and restricted or repetitive behaviors that do not meet criteria for a pervasive developmental disorder diagnosis (Dawson et al., 2002; Folstein et al., 1999; Piven, Palmer, Jacobi et al., 1997). Previous work has demonstrated that families with ASDs show an increased rate of BAP (12% to 25%). Compared with other clinical diagnoses such as Down syndrome, parents of autistic individuals manifest these traits 50% of the time compared with 2% seen in Down syndrome (Piven & Palmer, 1997; Piven, Palmer, Jacobi et al.; Szatmari, Jones et al.).

Since the BAP describes subclinical features, traditional diagnostic measures are generally not sensitive enough to assess the BAP. However, measures appropriate for assessing the BAP are being created. For example, the Social Responsiveness Scale, which is described below, is a quantitative measure of social ability, ranging continuously from significantly impaired to above-average abilities (Constantino, 2002). Social deficits characteristic of ASDs are common and may be viewed on a continuum with possible cutoffs for affected individuals (Constantino & Todd, 2003). In a large twin sample, Constantino and Todd found a substantial shift in the distribution of scores towards the pathological end in children from families in which both parents manifest subthreshold autistic traits.

Identifying individuals with the BAP and examining their neurocognitive development may help in understanding similarities and differences between these family members and their relatives with and without ASDs. This may also help in identifying patterns of cognition and development that are endophenotypes of ASDs, which are critical in identifying the genetic etiology (or etiologies) of this complex disorder.

Intellectual Profiles in Autism Spectrum Disorders Family Members

IQ patterns in family members of those with ASDs have been studied with mixed results. Higher VIQ scores and discrepancies in favor of verbal scores have been found in first-degree relatives of individuals with autism (Fombonne, Bolton, Prior, Jordan, & Rutter, 1997). Folstein et al. (1999) found lower FSIQs and PIQs with decreased performance on the picture arrangement and picture completion tasks in parents of children with autism compared with parents of Down syndrome children. These findings were not, however, replicated in the ASD or Down syndrome siblings, suggesting that age or other factors may play a role (Folstein et al.). Finally, Szatmari et al. (1996) found high intraclass correlations between IQ and an index of social behavior among autistic siblings with autism and low intraclass correlations among similar variables when comparing affected and unaffected siblings. This finding suggests that IQ alone may not be meaningful when studying phenotypes.

These previous studies of IQ in families were conducted before the concept of the BAP was introduced. Thus, they likely combined family members with and without the BAP in analyses. In a study comparing family members with the BAP with those without, Fombonne et al. (1997) found significantly lower IQ scores and poorer reading and spelling abilities in individuals with the BAP. Thus, further research is needed to understand the relationship between the BAP and neurocognitive profiles.

Language Profiles in Autism Spectrum Disorders Families

Language in ASD has a strong genetic etiology (Newbury et al., 2002; Rapin, 1996; Silverman et al., 2002; Wassink & Piven, 2000), possibly being one of the most heritable aspects of the disorder. Several researchers have found that family members of those with ASD demonstrate language impairments of a similar nature (Piven, Palmer, Jacobi et al., 1997; Plumet, Goldblum, & Leboyer, 1995; Wolk & Edwards, 1993). Building upon studies demonstrating heritability of language in autism, recent work has explored potential phenotypes in families; however, findings have not been consistent and have mostly utilized autism diagnostic measures rather than broader measures that would capture more subtle language deficits. Recently, stratification of ASD families by language delay (as grossly indicated by the Autism Diagnostic Interview-Revised) has been explored in genetic linkage studies, producing strengthened signals on chromosome 2q (Bradford, 2001; Buxbaum et al., 2001; Shao et al., 2002). Bradford also reported

linkage signals on chromosomes 7 and 13 based on examining parents with speech delay. However, these findings have not been replicated consistently (Spence et al., 2006). A potential explanation is that broader and more sensitive language measures are needed in order to more accurately capture the phenotype of language deficits in ASD.

Summary

The DSM-IV-TR diagnoses of autistic disorder, Asperger disorder, and pervasive developmental disorders-not otherwise specified do not identify distinct, homogeneous subgroups; thus, they tell little about possible etiologies or predictors of outcome in ASDs (American Psychiatric Association, 2000). Subtypes of ASDs might be more clearly illuminated by studying factors outside the current diagnostic criteria such as cognitive profiles and developmental trajectories. Previous studies of neurocognitive profiles in ASD have found a range of different patterns, but this may be due to a limited understanding of the relationship among age, developmental course, and neurocognitive ability. If researchers can understand these patterns more fully, they may find similar profiles at the subclinical level in family members. Identifying such ASD subtypes and endophenotypes will help further studies of genetic etiology.

The Present Study

The present study examined the cognitive and behavioral profiles of 303 individuals from families with one or more members with an ASD in order to

identify potential subtypes. Since the purpose was to explore variables outside the current diagnostic criteria, variables were included that are known to impact the clinical presentation of ASDs and to vary widely among individuals with ASDs. Then an exploratory approach was utilized to identify possible multidimensional profiles.

Constructs representing measures of intelligence, language, social ability, adaptive functioning, and maladaptive behavior were used in a cluster analysis. First, the affected family members were examined, and then results were compared with findings from the unaffected family members. This study is one of the first studies of the relationship between cognitive and behavioral variables in whole families with ASDs.

METHODS

Participants

Three-hundred three individuals from 43 ASD families were included in this study. Families were obtained from ongoing research at the Utah Autism Research Program. Sixty-five participants met DSM-IV-TR criteria for autistic disorder, Asperger disorder, or pervasive developmental disorder-not otherwise specified and are referred to as "affected" individuals (M = 16.01 years old, SD = 10.63; American Psychiatric Association, 2000). The remaining 238 individuals were "unaffected" relatives who did not meet criteria for any pervasive developmental disorders (M = 38.76 years old, SD = 18.49). Most families include more than one affected individual. However, approximately 10 nuclear families contain only one affected member but are part of a large extended pedigree with four to seven cases of ASD.

Participants ranged in age from 72 months to 58 years. Approximately 92% of the participants were Caucasian or White, 1% were Hispanics, .01% were American Indian/Alaska Native, .07% were Asian, .02% were Native Hawaiian or other Pacific Islander, and .04% were Black or African American.

All participants were recruited through the Utah Autism Research Program at the University of Utah and were part of ongoing studies. The Utah Autism Research Program is a widely known local research program; interested families

contact the Utah Autism Research Program and are screened to determine eligibility. Participants are excluded if they meet one of the following criteria: (a) have a known medical condition or genetic disorder associated with ASD characteristics (e.g., fragile X syndrome, congenital rubella, tuberous sclerosis, and phenylketonuria; (b) are adopted or have no biological parent available to participate; and (c) have severe sensory impairments that would prevent participation in direct testing.

Measures

Intellectual Functioning

Differential Abilities Scale

The Differential Abilities Scale (Elliott, 1990) is an individually administered cognitive and achievement test for those aged 36 months to 17 years 11 months (see Table 1). The scale is appropriate for children with either delayed or normal development and was designed to provide a single measure that can be used to identify the full range of cognitive functioning from intellectually impaired to gifted. The Differential Abilities Scale is divided into three levels: (a) lower preschool (ages 2 years, 6 months through 3 years, 5 months); (b) upper preschool (ages 3 years, 6 months through 5 years, 11 months); and (c) school age (ages 6 years, 0 months through 17 years, 11 months). The Differential Abilities Scale yields an overall general conceptual ability score and domain scores in the areas of verbal cluster and spatial cluster. Specific subtests include block building, verbal comprehension, picture similarities, naming vocabulary, pattern construction, early

Table 1

Composite IQ

Test	CVIQ (composite verbal IQ)	CPIQ (composite performance IQ)	COIQ (composite overall IQ)
DAS: Standard administration			
Preschool DAS ages 2:6 to 3:5	N/A	N/A	Lower level general conceptual ability score (LLGCA; mean = 100, *SD* = 15)
Preschool DAS ages 3:6 to 5:11	Verbal ability (cluster score; Table 2 in manual; mean = 100, *SD* = 15)	Nonverbal ability (cluster score; Table 2 in manual; mean = 100, *SD* = 15)	Upper level GCA standard score (mean = 100, *SD* = 15)
DAS: Administration for lower-functioning individuals			
Ages 2:9 to 6:11 who receive the four core subtests of the lower preschool level battery (above age 6:11 use 6:11 norms)	N/A	N/A	Extended GCA (IQ estimate; see Table 5, p. 385 of DAS manual; IQ estimate in the form of mean = 100, *SD* = 15)
Ages 6:3 to 17:11 who receive the six core subtests of the school-age level battery (above age 17:11 use 17:11 norms)	N/A	N/A	Extended GCA (IQ estimate; see Table 5, pp. 388-389 of DAS manual; IQ estimate in the form of mean = 100, *SD* = 15)
DAS: Administration for individuals who are hearing impaired or language impaired to the point that verbal subtests are inappropriate	N/A	Special nonverbal composite (nonverbal IQ estimate in the form of mean = 100, *SD* = 15)	N/A

Table 1 (*continued*)

Test	CVIQ (composite verbal IQ)	CPIQ (composite performance IQ)	COIQ (composite overall IQ)
Mullen *T* scores are converted to standard scores (mean = 100, *SD* = 15)	Receptive language (converted standard score: mean = 100, *SD* = 15) + ExpressLang (converted standard score: mean = 100, *SD* = 15)/2	Visual reception (converted standard score: mean = 100, *SD* = 15) + fine motor (converted standard score: mean = 100, *SD* = 15)/2	Early learning composite (converted standard score: mean = 100, *SD* = 15)
WAIS-III	VCI (mean = 100, *SD* = 15)	POI (mean = 100, *SD* = 15)	FSIQ (mean = 100, *SD* = 15)
WASI	VIQ (mean = 100, *SD* = 15)	PIQ (mean = 100, *SD* = 15)	FSIQ (mean = 100, *SD* = 15)
WISC-III	VIQ (mean = 100, *SD* = 15)	PIQ (mean = 100, *SD* = 15)	FSIQ (mean = 100, *SD* = 15)

number concepts, copying, and matching letter-like forms. Overall and domain scores are reported as standard scores with a mean of 100 and a standard deviation of 15. Subtest scores have a mean of 50 and a standard deviation of 10. Research has demonstrated that the general conceptual ability score, verbal cluster, and spatial cluster correlate well with the FSIQ, VIQ, and PIQ scores of the Wechsler Intelligence Scale for Children-Third Edition (Dicerbo & Barona, 2001; Dumont, Cruse, Price, & Whelley, 1996). The Differential Abilities Scale has been used in studies of cognitive functioning in ASD (Joseph et al., 2002). For the current study, affected participants between the ages of 3 and 16 years were administered the Differential Abilities Scale. Low-functioning adults with an ASD were administered the Differential Abilities Scale if they were unable to complete the Wechsler Adult Intelligence Scale-Third Edition, which is described below. In addition, unaffected family members who were too young to take the Wechsler Abbreviated Scale of Intelligence, which is described below, were administered the Differential Abilities Scale.

Mullen Scales of Early Development

The Mullen Scales of Early Development (Mullen, 1995) is a standardized measure of cognitive functioning from birth through 68 months. The Mullen Scales of Early Development provides an overall early learning composite and five subdomain scores (gross motor, fine motor, visual reception, expressive language, and receptive language). Overall and domain scores are reported as *t* scores, with a mean of 50 and a standard deviation of 10. The Mullen Scales of Early

Development has proven to be a useful tool for examining young children with ASD (Akshoomoff, 2006; Landa & Garrett-Mayer, 2006). The Mullen Scales of Early Development was administered to those who were too young to complete the Differential Abilities Scale.

Wechsler Abbreviated Scale of Intelligence

The Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999) provides an IQ estimate based on four subtests used in the Wechsler Adult Intelligence Scale-Third Edition and Wechsler Intelligence Scale for Children-Fourth Edition. The Wechsler Abbreviated Scale of Intelligence is appropriate for individuals ages 6 through 89. The four subtests include vocabulary, similarities, block design, and matrix reasoning. The Wechsler Abbreviated Scale of Intelligence yields an overall FSIQ as well as VIQ and PIQ estimates. Each subtest is reported as a standard score with a mean of 100 and a standard deviation of 15. The Wechsler Abbreviated Scale of Intelligence has been widely used in healthy and clinical populations (Brooks & Weaver, 2005; Ringe, Saine, Lacritz, Hynan, & Cullum, 2002; Wymer, Rayls, & Wagner, 2003) and has been demonstrated to be a reliable measure in individuals with ASD (Minshew, Turner, & Goldstein, 2005). Although one study suggested the Wechsler Abbreviated Scale of Intelligence may not provide an accurate IQ in individuals with atypical IQ profiles (Axelrod, 2002; Saklofske, Hildebrand, & Gorsuch, 2000), a thorough study of the Wechsler scales in ASD demonstrated that they were appropriate for this population (Minshew et al.). The Wechsler Abbreviated Scale of Intelligence was administered to

unaffected family members ages 6 or older.

Wechsler Intelligence Scale for Children-Third Edition

The Wechsler Intelligence Scale for Children-Third Edition (Wechsler, 1991) is a widely used measure of intellectual functioning in children ages 6 through 16 years. The Wechsler Intelligence Scale for Children-Third Edition provides four composite scores (verbal comprehension index, perceptual reasoning index, working memory index, and processing speed index) and a FSIQ. The scale yields standard scores with a mean of 100 and a standard deviation of 15. The Wechsler Intelligence Scale for Children-Third Edition has been widely used in autism research (Billstedt, Gillberg, & Gillberg, 2005; Koyama, Tachimori, Osada, & Kurita, 2006) and has been demonstrated to be a useful measure of intelligence for individuals with ASD (Mayes & Calhoun, 2003, 2004).

Wechsler Adult Intelligence Scale-Third Edition

The Wechsler Adult Intelligence Scale-Third Edition (Wechsler, 1997) is a widely used measure of adult intelligence. The scale yields an overall FSIQ, VIQ, and PIQ as well as four composite scores (verbal comprehension, perceptual organization, working memory, and processing speed). Like the Wechsler Intelligence Scale for Children-Fourth Edition, this scale provides standard scores with a mean of 100 and a standard deviation of 15. Although the Wechsler Adult Intelligence Scale-Third Edition has demonstrated significant reliability and validity (Wechsler), it may be less reliable in examining low-functioning individuals

(FSIQ < 70; Jones, van Schaik, & Witts, 2006). The Wechsler Adult Intelligence Scale-Third Edition has been used in research studies that include individuals with ASD (Koyama, Tachimori, Osada, Takeda, & Kurita, 2007). The scale was administered to affected participants ages 18 and older.

Diagnostic

Autism Diagnostic Observation Schedule-Generic

The Autism Diagnostic Observation Schedule-Generic (Lord et al., 2000) is a semistructured, standardized assessment of domains related to the diagnosis of autism. The scale is appropriate for a wide range of ages and ability levels, from individuals with a mental age of approximately 12 months to high-functioning adults. The Autism Diagnostic Observation Schedule-Generic includes four modules that are designed to be administered to individuals based on their overall level of expressive language. An algorithm is used to derive an overall score, which is the sum of two domain scores (social and communication). Cutoff scores for autism and pervasive developmental disorders-not otherwise specified are provided. The Autism Diagnostic Observation Schedule-Generic is widely used in autism research and is the gold-standard instrument for a standardized direct observation measure. Researchers must establish reliability in administration and ratings with the original authors or with a research-reliable supervisor (e.g., Dr. Miller). The Autism Diagnostic Observation Schedule-Generic was used to aid in determining whether family members meet criteria for an ASD.

Autism Diagnostic Interview-Revised

The Autism Diagnostic Interview-Revised (Lord, Rutter, & Le Couteur, 1994) is an in-depth parent interview of the child's early developmental history. The Autism Diagnostic Interview-Revised is designed to complement the Autism Diagnostic Observation Schedule-Generic, and it maps directly into DSM-IV-TR criteria (American Psychiatric Association, 2000). The Autism Diagnostic Interview-Revised gathers extensive information about the triad of impairments associated with autism: (a) reciprocal social interaction, (b) communication and language, and (c) restricted and repetitive stereotyped interests and behaviors. An algorithm is provided with cutoff scores suggestive of autism within each of the three domains. Researchers must establish reliability in administration and rating with the original authors or with a research-reliable supervisor (e.g., Dr. Miller). In addition to the Autism Diagnostic Observation Schedule-Generic, the Autism Diagnostic Interview-Revised was used to aid in determining whether family members meet criteria for an ASD.

Social Ability

Social Responsiveness Scale

The Social Responsiveness Scale (Constantino, 2002) is a 65-item questionnaire that measures social ability. Parents complete the questionnaire on children, and a familiar adult completes the questionnaire on adults; that is, the scale is not self-rated. The Social Responsiveness Scale is a continuous measure with scores that range from severely impaired to above average. The scale yields

an overall score and domain scores in the areas of social awareness, social cognition, social communication, social motivation, and social mannerisms. Each domain yields a *t* score with a mean of 50 and standard deviation of 10. Scores above 60 are generally seen in high-functioning individuals with ASD and scores above 76 are strongly associated with a diagnosis of autism; thus, there is a wide range of scores seen in unaffected individuals. This measure is a relatively new but promising measure of ASD-related traits across the autism spectrum. Initial studies have shown significant family resemblance using these measures in autism families (Constantino, 2002; Dawson et al., 2007). The Social Responsiveness Scale was used as a measure of the BAP in unaffected family members and as a measure of social ability in affected members as it is capable of measuring both the BAP and autism traits.

Language

Clinical Evaluation of Language Fundamentals

The Clinical Evaluation of Language Fundamentals (Perez et al., 1995; Wiig, Secord, & Semel, 1992) is a widely used standardized test of language ability. The Clinical Evaluation of Language Fundamentals was designed to measure morphology, syntax, semantics, and working memory for language. The scale provides an overall score as well as separate expressive and receptive language scores, each with a mean of 100 and a standard deviation of 15. There is a preschool version for children between the ages of 3:0 and 6:11 and a school-age version for children between the ages of 6:0 and 21:11. The Clinical Evaluation of

Language Fundamentals has been shown to be a useful measure of language in individuals with ASD (Condouris, Meyer, & Tager-Flusberg, 2003; Kjelgaard & Tager-Flusberg, 2001; Tager-Flusberg, 2004). The Clinical Evaluation of Language Fundamentals has also been used to examine the language abilities of unaffected siblings (Pilowsky, Yirmiya, Shalev, & Gross-Tsur, 2003).

Expanded Token Test

The Expanded Token Test (Morice & McNicol, 1985) detects fine degrees of impairment in comprehension for syntax. The Expanded Token Test is based on the short, 36-item De Renzi and Faglioni (1978) version, but it also includes 27 new commands. The new commands consist of sentences more syntactically complex than those in the shorter version. The test was designed for use in patients with schizophrenia to assess comprehension of syntax. The Expanded Token Test yields an overall score ranging from 0 to 65. Individuals with autism demonstrate a wide range of language impairment, including impairment in syntax comprehension (Rapin & Dunn, 2003). In their study, the Expanded Token Test was used for individuals ages 20 and up as a measure of language functioning analogous to the receptive domain of the Clinical Evaluation of Language Fundamentals.

Adaptive Functioning

Vineland Scales of Adaptive Functioning

The Vineland Scales of Adaptive Functioning (Sparrow, Balla, & Cicchetti, 1984) is a semistructured interview that assesses personal and social skills in

individuals birth through 18 years, 11 months, including low-functioning adults. The interview is done with the primary caregiver and results in subdomain scores of (a) communication (receptive, expressive, and written); (b) daily living skills (personal, domestic, and community); and (c) socialization (interpersonal relationships, play and leisure time, and coping skills). The Vineland Scales of Adaptive Functioning also yields an overall adaptive behavior composite score. For the purposes of this study, the Vineland Scales of Adaptive Functioning was administered to all affected individuals. The communication, daily living skills, and socialization domains were included as measures of adaptive behavior.

Behavior

Aberrant Behavior Checklist

The Aberrant Behavior Checklist (Aman & Singh, 1986) is a symptom checklist that assesses problem behaviors in developmentally challenged individuals within multiple settings. Fifty-eight items form five subscales (irritability/agitation, lethargy/social withdrawal, stereotypic behavior, hyperactivity/noncompliance, and inappropriate speech). This checklist is designed to be used in individuals ages 6 through 54 years old. For the purposes of this study, the Aberrant Behavior Checklist was administered to all affected individuals and their siblings.

Variables

Variables Included in Cluster Analysis

Verbal, Performance, and Difference IQ Scores

The VIQ, PIQ, and difference IQ (VIQ-PIQ), based on composite IQ scores, was used as a variable in the cluster analysis for both affected and unaffected family members (see Table 1).

Social Abilities

The Social Responsiveness Scale total score was used to measure social abilities in both affected and unaffected family members.

Language Discrepancy Score

Depending on the language test administered (i.e., Clinical Evaluation of Language Fundamentals or Expanded Token Test), a discrepancy score (expressive–receptive) was calculated. For those administered the Clinical Evaluation of Language Fundamentals, the domain scores were used to calculate the discrepancy score. For those too old to be administered the Clinical Evaluation of Language Fundamentals, a discrepancy score was obtained from the Expanded Token Test (i.e., a measure of receptive language) and the VIQ was an estimate of expressive language. Therefore, the VIQ-Expanded Token Test total was the comparable discrepancy score used for those administered the Expanded Token Test.

Vineland Scales of Adaptive Functioning

The three domains obtained from the Vineland Scales of Adaptive Functioning were used in the cluster analysis for affected individuals only. These domains are (a) communication, (b) daily living, and (c) socialization.

Aberrant Behavior Checklist

The five domains from the Aberrant Behavior Checklist were included in the cluster analysis for affected individuals only. These domains include (a) irritability/agitation, (b) lethargy/social withdrawal, (c) stereotypic behavior, (d) hyperactivity/noncompliance, and (e) inappropriate speech.

Variables Used in Post Hoc Analysis

Age

Chronological age in months at the date of IQ testing was used as in the post hoc analyses.

Sex

Participants were identified as either male or female as designated by a categorical value (e.g., 0 or 1). This variable was then included in post hoc analyses as a covariate.

IQ Test Type

Since multiple IQ tests are used depending on age and ability level, each test was coded as a categorical value and included as a categorical covariate in the

post hoc analyses.

Language Test Type

As there were two measures of language included in the analyses, a categorical variable was created to ensure that the effects of which language test was given were considered.

Procedure

Participants came to the Utah Autism Research Program and were administered the research battery of assessments and a blood sample was taken (for other studies). The battery of tests administered was determined based on the participant's age, affection status, and ability level. The mother or primary caregiver completed the majority of the interviews and questionnaires for the family. Informed consent was obtained before participation. All study procedures were approved by the Institutional Review Board (#IRB00006042).

Preliminary Analyses

Prior to conducting the cluster analysis, several relevant data issues were examined. First, the distribution of each variable by age was examined. For the affected and unaffected groups, the distribution of all variables was plotted by age in order to determine that each variable was distributed evenly across the age range. This appeared to be true for all variables except the Aberrant Behavior Checklist in the affected group; it appeared that the Aberrant Behavior Checklist domains were skewed negatively, indicating that affected individuals obtained

scores mostly in the clinical range. As this would be expected, the data were not transformed.

Second, correlations among variables were examined (see Tables 2 and 3). This was done in order to determine whether inclusion of correlated variables would result in overweighting of the underlying construct in the cluster analysis. Weighting variables might be appropriate when testing a specific hypothesis, but it has been strongly argued against in exploratory cluster analysis research since the most appropriate way to explore similarity would be to give each construct equal weight (Sneath & Sokal, 1973). Redundant variables would also result in overweighting of the underlying trait and is not recommended in exploratory cluster analysis. In performing bivariate correlations, it was found that the total, expressive, and receptive domain scores of the Clinical Evaluation of Language Fundamentals were highly correlated with VIQ. If included, the results would be biased toward overemphasizing the role of language in determining the clusters. Thus, the Clinical Evaluation of Language Fundamentals total and domain scores were removed from analysis, but the discrepancy score between receptive and expressive language domains was retained.

Third, standardization of variables was considered. Standardizing variables is a common procedure in cluster analysis since using unstandardized variables may inadvertently weigh variables differently, thus affecting results. In this study, all variables, with the exception of scores from the Aberrant Behavior Checklist and Expanded Token Test, came from standardized tests developed on typical

Table 2

Affected Family Members: Correlations

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
1.AGE																								
2. VIQ	.311*																							
3. NVIQ	.207*	.678*																						
4. FSIQ	.250*	.877*	.923**																					
5. VIQ-NVIQ	0.166	.461*	-.328**	0.016																				
6. CELF RECEPTIVE	0.099	.783*	.663**	.779**	.268*																			
7. CELF EXPRESSIVE	0.134	.801*	.600**	.739**	.370**	.901*																		
8. CELF TOTAL	0.105	.799**	.642*	.770**	.313**	.966**	.963**																	
9. CELF EXPRESSIVE-RECEPTIVE	0.06	-.113	-.259**	-0.233*	.171	-.403*	.035	-.193																
10. TOKEN	0.066	.648**	.645**	.768**	-.112	.843*	.816*	.824*	.674															
11. SRS TOTAL	-0.159	-.172	-.138	-.191	-.062	-.072	-.090	-0.12	-.019	-.273														
12. SRS_AWARE_TOTAL	-0.121	-.144	-.147	-.204*	.005	.019	.023	-.008	.010	-0.254	.711*													
13. SRS_COG_TOTAL	-0.234*	-.276*	-.232*	-.267*	-.100	-.094	-.92	-.118	.030	-.447*	.858*	.617**												
14. SRS_COMM_TOTAL	-0.112	-.141	-.127	-.145	-.024	.004	.016	-.022	.032	-.288	.903*	.749**	.807*											
15. SRS_MOTIV_TOTAL	0.132	.006	-.029	-.049	.062	.025	-.009	-.010	-.084	-.031	.721*	.583**	.549*	.705**										
16. SRS_MANNER_TOTAL	-0.101	-.206	-.214	-.252*	-.007	-.071	-.111	-.130	-.072	-.444*	.844*	.700**	.746*	.750**	.619**									
17. VINELAND_COMMUN_DOMAIN	-0.115	.376*	.429**	.537**	-.009	.386**	.359**	.371**	-.133	.684**	-.274*	-.217*	-.324*	-.270*	-.210	-.318**								
18. VINELAND_DAILY_SKILLS_DOMAIN	.331**	.432*	.369**	.497**	.151	.264*	.304**	.293*	.037	,538*	-.366*	.329**	-.410*	-.380**	-.209	-.435**	.730**							
19. VINELAND_SOCIALIZATION_DOMAIN	0.035	.171	.224*	.300*	-.031	.036	.031	.042	-.016	.491*	-.374*	-.404**	-.298*	-.441**	-.374**	-.394**	.628**	.705**						
20. ABC_IRRITABILITY	-0.319*	-.040	-.114	-.042	.079	.061	.095	.060	.068	-.160	.487*	.370**	.564*	.469**	.329**	.540**	.031	-.202	-.163					
21. ABC_LETHARGY	0.023	.061	.110	.090	-.053	.123	.071	.068	-.116	.015	.550*	.555**	.381*	.568**	.717**	.594**	-.051	-.188	-.274*	.424**				
22. ABC_STEREOTYPE	-0.078	-.274**	-.222*	-.245*	-.088	-.107	-.129	-.144	-.037	-.273	.504*	.486**	.532*	.509**	.473**	.688**	-.173	-.271*	-.228	.539**	.573*			
23. ABC_HYPERACTIVITY	-0.350*	-.181	-.257*	-.170	.071	.063	.028	.017	-.076	-.320	.477*	.440**	.542*	.492**	.197	.598**	-.022	-.260*	-.156	.788**	.347*	.584*		
24. ABC_INAPPROPRIATE_SPEECH	-0.137	-.283**	-.270	-.289**	-.042	-.137	-.289*	-.250*	-.306*	-.561**	.402*	-.008	.428*	.352**	.237*	.539**	-.209	-.314**	-.147	.481**	.323*	.562*	.518*	-

*Significant at the $p > .05$ level.

**Significant at the $p > .001$ level.

Table 3

Unaffected Family Members: Correlations

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1.AGE																
2. VIQ	.053															
3. NVIQ	.044	.505**														
4. FSIQ	.053	.840**	.858**													
5. VIQ-NVIQ	.000	.351**	-.631**	-.175**												
6. CELF RECEPTIVE	-.275*	.316*	.425**	.473**	-.097											
7. CELF EXPRESSIVE	.123	.580**	.310*	.559**	.229	.481**										
8. CELF TOTAL	-.104	.413**	.435**	.542**	-.022	.398**	.604**									
9. CELF EXPRESSIVE-RECEPTIVE	.400**	.157	-.190	-.029	.300*	-.661**	.340*	.090								
10. TOKEN	-.077	.448**	.382**	.475**	-.057	.928	.851	.998*	-.940							
11. SRS TOTAL	.018	-.119*	-.056	-.096	-.043	-.060	-.193	.040	-.150	-.169*						
12. SRS_AWARE_TOTAL	.068	-.072	-.029	-.049	-.031	-.032	-.015	.011	.019	-.099	.767**					
13. SRS_COG_TOTAL	.072	-.156**	-.079	-.136*	-.050	-.087	-.183	.011	-.108	-.184*	.878**	.665**				
14. SRS_COMM_TOTAL	-.008	-.130*	-.067	-.107	-.040	-.054	-.232	.031	-.202	-.155*	.935**	.708**	.785**			
15. SRS_MOTIV_TOTAL	-.049	-.091	-.009	-.052	-.089	-.056	-.186	.094	-.147	-.119	.845**	.588**	.632**	.764**		
16. SRS_MANNER_TOTAL	.030	-.063	-.042	-.044	-.009	-.030	-.136	.032	-.120	-.127	.830**	.594**	.720**	.698**	.610**	-

populations. Norms are not available for the Aberrant Behavior Checklist. Since the checklist was developed for a population of individuals with developmental disabilities rather than a typical population, standardizing scores was not desirable. Thus, raw scores were used for the Aberrant Behavior Checklist.

The Clinical Evaluation of Language Fundamentals is not normal for adults; therefore, the Expanded Token Test was included as a measure of receptive language. Since verbal IQ correlated so highly with the Clinical Evaluation of Language Fundamentals expressive domain score in children, the VIQ was utilized as a measure for expressive language in adults. The discrepancy between the VIQ and the Expanded Token Test was calculated. Since the Expanded Token Test was developed for individuals with schizophrenia and norms based on typically developing populations have not been developed, norms were created for the Expanded Token Test based on data from all unaffected individuals in the present study in order to examine scores on the same scale as other variables. First, unaffected individuals were broken down into the same age groups used for the Wechsler Adult Intelligence Scale-Third Edition norms (Wechsler, 1997). Then the age groups were examined for outliers. Since their scores were so low that they would have resulted in a negative standard score, individuals with scores below 30 were excluded (one individual in each age group). Means and standard deviations were then determined for each age group, and standard scores (M = 100, SD = 15) were created from raw scores. Standard scores at or below 50 were converted to 50, as all other measures utilizing standard scores (e.g., IQ and language) used

a floor of 50. Again, the purpose of this data standardization was to convert Expanded Token Test raw scores into scores that would be comparable to other standard scores used in the analysis. While some uniqueness of the raw data would be lost in the process, this would ensure the most accurate comparison of scores.

Standardized scores (M = 100, SD = 15) were used for all other variables (see Table 4). In other words, I did not standardize scores for the cluster analysis, and the results would be able to be compared against those in the unaffected (i.e., nonclinical) sample.

Table 4

Reference Table: Scores for Each Measure

	Mean	*SD*	Transformed	Original mean, *SD*
IQ tests	100	15	Yes	See Table 2
VIQ-NVIQ	Raw score	N/A	Yes	See Table 2
Clinical Evaluation of Language Fundamentals-III	100	15	No	N/A
Clinical Evaluation of Language Fundamentals-Preschool	100	15	No	N/A
Expanded Token Test	100	15	Yes	Raw score (0 to 65)
Age	Raw score	N/A	No	N/A
Social Responsiveness Scale	100	15	Yes	M = 50, SD = 10
Aberrant Behavior Checklist	Raw score	N/A	No	Raw score
Vineland Scales of Adaptive Functioning	100	15	No	N/A

Finally, each variable was screened for outliers. Removing outliers is recommended in order to improve accuracy of the Ward (1963) cluster solution, which is described below (Comrey, 1985; Hair, Anderson, Tatham, & Black, 1998). A score was considered an outlier if it was greater than three standard deviations above or below the mean. No outliers were identified.

Cluster Analysis

Cluster analysis is a multivariate statistical procedure used to determine whether classifications exist in a particular dataset. By nature, cluster analysis is an exploratory approach; thus, it can be helpful in generating hypotheses regarding the grouping of variables. Cluster analysis has limitations as a statistical procedure because it can be difficult to validate cluster solutions (Morgan & Ray, 1995); thus, results should be interpreted with caution. However, cluster analysis was the appropriate procedure for the current study for several reasons. First, the purpose of this study was to identify possible cognitive and social profiles in families with ASD that might not have been previously considered rather than to test an a priori hypothesis or to identify a specified number of profiles. Second, cluster analysis has been described as a useful technique to examine multidimensional family data such as the current study (Henry, Tolan, & Gorman-Smith, 2005). The data included a large number of families with six types of measures. Cluster analysis provides a method that maximizes the within-group similarity and minimizes the between-group similarity. Finally, cluster analysis provides a useful method to analyze data that are not normally distributed. The current data were not

anticipated to be normally distributed; that is, individuals with autism might be expected to obtain scores in the clinical ranges or to obtain larger discrepancy scores for IQ and language abilities than seen in the general population. Thus, to accurately capture the natural distribution of the data, a method that does not assume a normal distribution was necessary. In summary, cluster analysis allows for a more exploratory way of examining data in which a predefined structure does not yet exist and in which the data are not normally distributed.

The cluster analysis involved three steps. First, clusters were identified using Ward's (1963) hierarchical agglomerative method. Several studies have recommended using a hierarchical agglomerative method (e.g., Ward) initially in order to identify the first seed points (Milligan, 1980; Waller, Kaiser, Illian, & Manry, 1998). Ward's method attempts to reduce the variance (sums of squares) between any two clusters and, thus, is more efficient compared with other methods. Ward's method also identifies a smaller number of clusters than other methods, which was preferred for the current study.

Once seed points were identified through Ward's (1963) method, the second step was to confirm the number of clusters using the *k*-means iterative method. The *k*-means method is a nonhierarchical method that is commonly used in combination with a hierarchical procedure (Ward) in order to determine whether the results from Ward's method converge with another different method. This method is a separate way to identify clusters and has been suggested as a confirmatory analysis of clusters selected by a hierarchical agglomerative method (Fisher & Ransom,

1995; Henry et al., 2005).

Third, an additional validation technique was applied. The unaffected group was split in half randomly and then reanalyzed separately as two groups. This method is a helpful validation technique when the sample size is large enough to permit splitting. Other techniques are also available, including reanalyzing the data using a different clustering method such as confirmatory cluster analysis, analyzing a different sample using the same technique in order to determine if the same clusters emerge, and testing the cluster solution on an external variable that would predict cluster membership according to prior research (Henry et al., 2005). However, the current sample of affected individuals was too small to permit splitting. There is no prior research to provide an external variable to predict cluster membership, and a separate sample was not available for comparison. Thus, the current study was limited to using *k*-means as a confirmatory analysis for both the affected and unaffected samples and splitting the unaffected sample into two groups analyzed separately.

The initial step in the current cluster analysis was to identify the ideal number of cluster solutions using Ward's (1963) hierarchical agglomerative method in the affected data. The range of cluster solutions for Ward's method was not specified a priori as the aim was to allow for the most natural clustering of the dataset. Squared Euclidian distance was used to determine the distance between the seed points and each of the other objects by using *z*-scores. Using squared Euclidian distance allows for greater weight to be put on objects that are farther

apart.

Ward's (1963) method resulted in a dendrogram of all participants and the relationship among potential clusters. Visualizing the dendrogram indicated that two to five clusters might be apparent. *K*-means at each potential step (e.g., two-cluster solution and three-cluster solution) suggested that the four-cluster solution yielded the most informative groupings. At the two-cluster level, large groupings were apparent that did not appear homogeneous; however, at the four-cluster level, each larger cluster had split into two more informative groupings. At the four-cluster level, IQ and adaptive functioning significantly impacted cluster membership. Beyond the four-cluster level, the groups appeared to be too small to interpret meaningfully.

The same method was applied to the unaffected family member data, except that split-half reliability methods were also utilized. Ward's (1963) method yielded a dendrogram that depicted two to four potential clusters. The *k*-means analysis suggested that the two-cluster solution was informative while remaining conservative. The *k*-means also revealed potentially more interesting yet less valid clusters above the two-cluster level. This solution was then cross-validated by randomly splitting the sample and reanalyzing the data using both Ward's method and *k*-means. This time Ward's method clearly suggested the two-cluster solution for each sample, which was likely due to the smaller sample size and which was confirmed with the *k*-means procedure. The *k*-means procedure revealed the same two-cluster solution for each randomly split sample and confirmed the two-cluster

solution found in the entire sample. Measures of IQ, language, and social ability significantly impacted cluster membership beginning at the two-cluster level. This was true for the split samples as well; that is, measures of IQ, language, and social ability also significantly impacted cluster membership for each randomly split sample.

In summary, a four-cluster solution was found for the affected sample. For the unaffected sample, a two-cluster solution was identified.

RESULTS

Results from the cluster analysis are presented according to the aims previously described. First, the clusters are described for both the affected and unaffected family members. Second, post hoc between-cluster analyses are described for each sample. Finally, the results from post hoc analyses examining measures of sex, IQ, language test type, and family membership are described. Analyses were performed using SPSS 15 (SPSS, Inc. 2006).

Affected Family Members: Cluster Descriptions

All four clusters showed similar levels of social impairment as measured by the Social Responsiveness Scale, suggesting that all four groups showed similar levels of ASD behaviors. These groups also showed similar profiles on the Aberrant Behavior Checklist domains. Thus, these scores are not included in the group descriptions (see Tables 5 and 6).

Group 1: Average IQ, Low Adaptive

Group 1 contained 19 individuals or 29.23% of the sample and was defined by high cognitive scores and low adaptive functioning scores. This cluster's VIQ and PIQ were in the average range of performance. Their discrepancy IQ was considered minimal (VIQ-PIQ = 5) and their language discrepancy was also minimal (expressive-receptive = 8). However, their adaptive skills were in the

Table 5

Affected Family Members: Cluster Labels

	Cluster label	*N*	% of sample	Mean age
Cluster 1	Average IQ, low adaptive	19	29.23	18.50
Cluster 2	Lowest IQ, severe adaptive	7	10.77	14.58
Cluster 3	Low average IQ, mild-moderate adaptive	21	32.30	10.00
Cluster 4	Average IQ, average adaptive	18	27.69	21.00

Table 6

Affected Family Members: Final Cluster Centers

	Cluster			
	1	2	3	4
CVIQ	112	65	79	118
CPIQ	107	90	88	123
DIF_IQ	5.00	-25.14	-9.05	-4.44
LANG_DISCREP	8.09	.29	-6.52	-.71
SRS_STD_SCORE	146	155	141	135
VINELAND_COMMUN_ DOMAIN	66	45	80	104
VINELAND_DAILY_SKILLS_ DOMAIN	61	36	66	105
VINELAND_SOCIALIZATION_ DOMAIN	50	43	72	87
ABC_IRRITABILITY	12	12	12	10
ABC_LETHARGY	15	16	13	12
ABC_STEREOTYPE	4	5	5	4
ABC_HYPERACTIVITY	14	12	19	10
ABC_INAPPROPRIATE_ SPEECH	3	6	5	3

mildly to moderately impaired to severely impaired range. Within the adaptive domain, this group demonstrated slightly better communication and daily living scores compared with socialization scores.

Group 2: Lowest IQ, Severe Adaptive

Group 2 included 7 family members, which was the smallest cluster (N = 7, 10.77% of the sample) and the most severely impaired group. These members had the lowest VIQ (65), which was in the mildly to moderately impaired range, and an average PIQ (90), which yielded the largest discrepancy IQ in all of the groups (-25). Their language discrepancy score was minimal. Finally, this group demonstrated the poorest adaptive skills, which fell into the severely impaired range.

Group 3: Low Average IQ, Mild-to-Moderate Adaptive

Group 3 included 21 individuals or 32.30% of the sample. They demonstrated low average VIQ and average PIQ scores. They also demonstrated IQ and language discrepancy scores in the negative direction, indicating better PIQ and receptive language scores. This group's adaptive functioning profile demonstrated low average communication, mild to moderately impaired daily living skills, and borderline to mildly impaired socialization scores.

Group 4: Average IQ, Average Adaptive

Group 4 included 18 individuals or 27.69% of the sample. These individuals demonstrated high average VIQ and high average PIQ scores. They

also demonstrated small negative discrepancies in both IQ and language, suggesting better PIQ and receptive language scores. Their adaptive scores were all in the average range.

Unaffected Family Members

Two clusters were identified in the unaffected data (see Tables 7 and 8).

Group A: Truly Unaffected

This group consisted of 120 individuals or 50.40% of the sample. Their Social Responsiveness Scale scores were low, suggesting they did not have social impairments or other ASD characteristics. They demonstrated an even IQ profile with scores in the average range of performance and no discrepancy in IQ. However, they demonstrated a large language discrepancy in the positive direction, suggesting better expressive language scores.

Group B: Possible Broader Autism Phenotype

This group consisted of 118 individuals or 49.58% of the sample. They obtained an average social ability score in the moderate range, suggesting clinically significant deficiencies in reciprocal social interaction but at lower levels than typical of ASD. This group demonstrated VIQ and PIQ scores in the average range; however, their discrepancy IQ score was in the negative direction, suggesting better PIQ scores compared with VIQ scores. In terms of language discrepancy, this group demonstrated even skills.

Table 7

Unaffected Family Members: Cluster Labels

	Cluster label	*N*	% of sample	Mean age
Cluster 1	Unaffected	120	50.40	40.08
Cluster 2	Possible broader autism phenotype	118	49.58	37.42

Table 8

Unaffected Family Members: Final Cluster Centers

	Cluster	
	1	2
CVIQ	112	106
CPIQ	112	118
DIF_IQ	.36	-11.59
LANG_DISCREP_SCORE	12	1
SRS_STD_SCORE	86	106

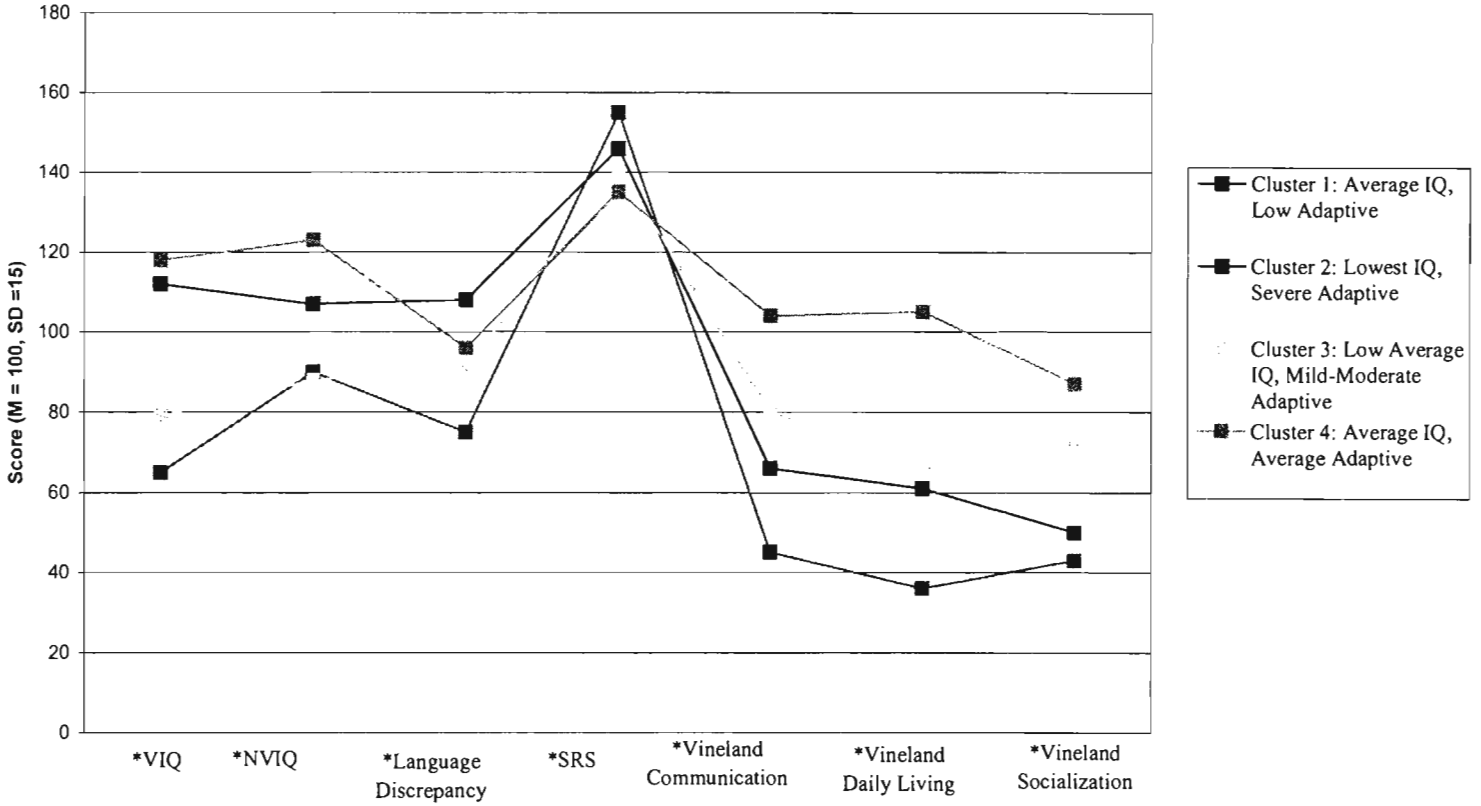
Post Hoc Between Cluster Differences

The Scheffé test was conducted for each sample in order to determine whether clusters differed significantly from one another. Since the Scheffé test tends to be conservative, inasmuch as it requires larger differences among means for significance than other methods, the Scheffé was selected as a post hoc test to compare group means. This test is ideal for data such as the current study as it was not a large sample and thus had little power left for post hoc analyses. This is

particularly true for the affected sample. The Scheffé test confirmed the four-cluster solution for the affected group data. The four clusters differed from other groups on each of the variables indicated in the Ward (1963) method (see Figures 1 and 2). For VIQ, Groups 1 and 4 were similar to each other ($p = 0.556$) but different from Groups 2 and 3; likewise, Groups 2 and 3 were similar to each other ($p = 0.120$) but different from Groups 1 and 4. The Scheffé test for PIQ indicated that Groups 1 and 3 ($p = 0.011$) and Groups 2 and 4 ($p < 0.001$) were different from one another. For discrepancy IQ, Groups 1 and 2 differed significantly from one another ($p = 0.002$). Similarly, for language discrepancy, Groups 1 and 3 differed significantly ($p = 0.045$) and all others were similar. For the measure of social ability, no clusters differed significantly. The Scheffé test for the adaptive functioning measures indicated that the Aberrant Behavior Checklist did not differ among any of the clusters, but the Vineland Scales of Adaptive Functioning domains differed significantly among all clusters with two exceptions: (a) Groups 1 and 3 did not differ on the daily living skills domain ($p = 0.806$) and (b) Groups 1 and 2 were similar on the socialization domain ($p = 0.580$).

Post Hoc Analyses for External Variables

The measures of age, sex, IQ test type, and language test type were examined post hoc in order to determine whether they affected group membership for each sample. The Scheffé test of between-group differences was used.



*Indicates that the variable significantly impacted cluster membership.

Figure 1. Affected sample: Cluster profiles.

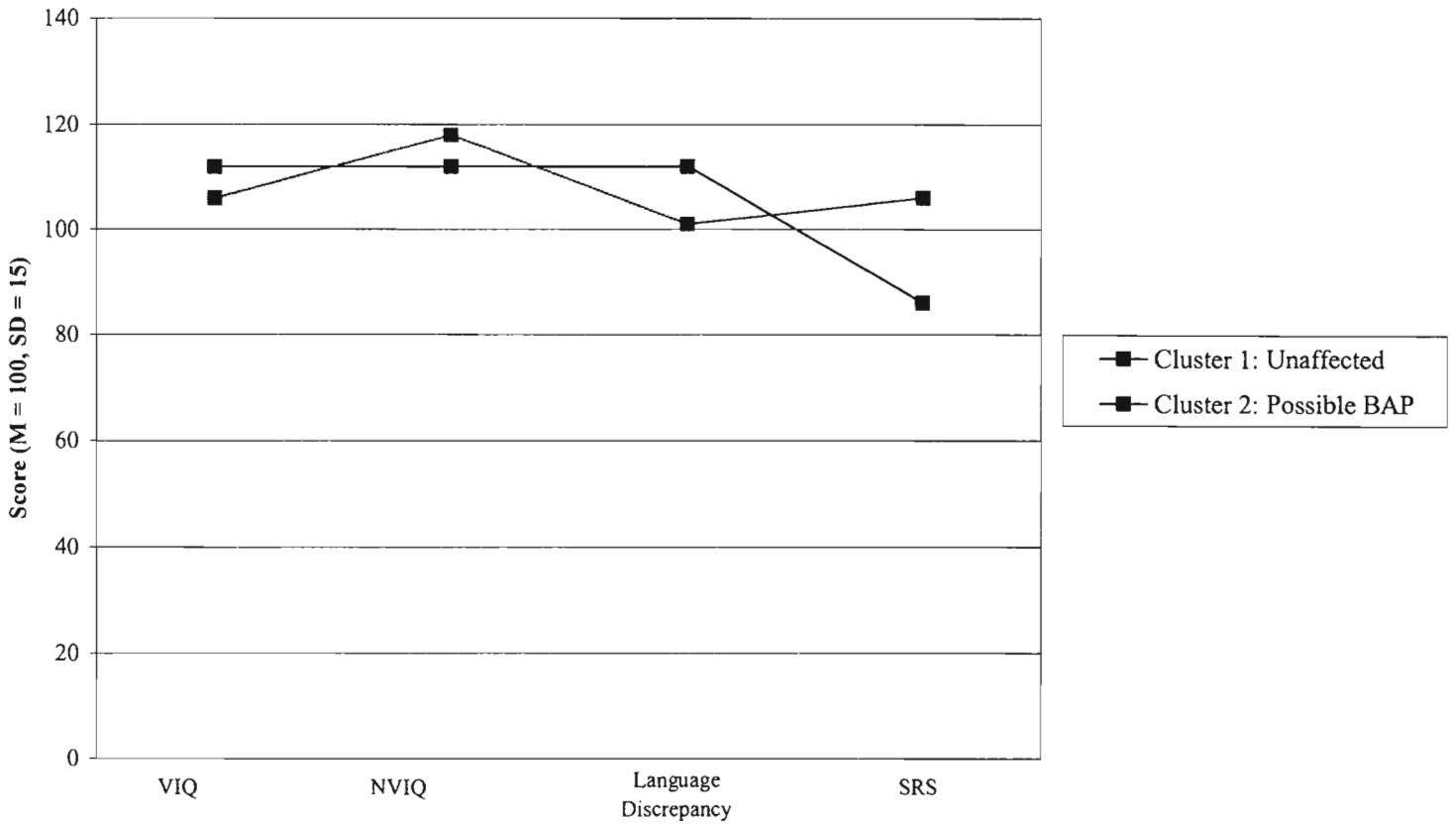


Figure 2. Unaffected sample: Cluster profiles.

Affected Group

The post hoc Scheffé test indicated that age, IQ, and language test type significantly impacted cluster membership for affected family members. For the Scheffé test, age significantly impacted cluster membership, $F(3) = 4.55$, $p < 0.05$ (see Table 9). However, tests of between-group differences indicated that significant differences for age were found between Groups 3 and 4 only ($p < 0.05$). IQ test type significantly impacted cluster membership, $F(3) = 5.400$, $p < 0.005$. Specifically, post hoc analyses of the cluster effect indicated that Groups 1 and 3 were significantly different in terms of IQ test type (see Table 10). Similarly, language test type also appeared to significantly impact cluster membership, $F(3) = 4.764$, $p = 0.005$, with Groups 1 and 3 differing significantly (see Table 11). Sex did not appear to impact cluster membership, $F(3) = 1.537$, $p = 0.214$ (see Table 12).

Table 9

Affected Data: Average Age and Cluster Membership

	Mean age in years	*SD*
Cluster 1	18.53	9.417
Cluster 2	14.583	8
Cluster 3	10	5.25
Cluster 4	21	14.083

Table 10

Affected Data: IQ Test Type and Cluster Membership

	DAS preschool	DAS school age	WASI	WAIS-III	WISC-III
	Count	Count	Count	Count	Count
Cluster 1		7	1	9	2
Cluster 2		5		2	
Cluster 3	1	18		2	
Cluster 4		10		8	

Table 11

Affected Data: Language Test Type and Cluster Membership

	CELF-Preschool	CELF-III	Expanded Token Test
	Count	Count	Count
Cluster 1		13	6
Cluster 2		5	2
Cluster 3	3	18	
Cluster 4		13	5

Table 12

Affected Data: Sex Differences in Cluster Membership

	Male	Female
	Count	Count
Cluster 1	14	5
Cluster 2	7	
Cluster 3	17	4
Cluster 4	17	1

Unaffected Family Member Data

The post hoc Scheffé test indicated that none of the external measures impacted cluster membership for the unaffected data. Clusters did not differ based on age, sex, IQ test type, or language test type (see Tables 13, 14, 15, and 16).

In summary, post hoc tests indicated that the affected data were impacted by age, IQ, and language test type. This was not the case for the unaffected data as cluster membership did not differ based on any of the above variables.

Table 13

Unaffected Data: Average Age and Cluster Membership

	Mean age in years	*SD*
Cluster 1	40.083	19
Cluster 2	37.417	17.917

Table 14

Unaffected Data: Sex and Cluster Membership

	Cluster number of case	
	1	2
Male	50	57
Female	70	61

Table 15

Unaffected Data: IQ Test Type and Cluster Membership

	DAS school age	WASI	WAIS-III
	Count	Count	Count
Cluster 1		120	
Cluster 2	3	112	3

Table 16

Unaffected Data: Language Test Type and Cluster Membership

	CELF-Preschool	CELF-III	Expanded Token Test
	Count	Count	Count
Cluster 1		22	98
Cluster 2	3	20	95

DISCUSSION

The present study examined the behavioral and cognitive profiles in individuals with ASD and their family members. This study is one of the first to examine the relationship between behavioral and cognitive variables in whole families with ASD. The first aim of the study was to examine constructs of intelligence, language, social ability, adaptive functioning, and maladaptive behavior in the affected family members using cluster analysis. The second aim was to compare the identified profiles with those in the unaffected family members by examining similar constructs using the same method. Four clusters emerged for the affected family members and two clusters emerged for the unaffected family members. The value of utilizing this profile approach was that it captured those individuals who demonstrated unevenness across the various constructs. This is often difficult to observe in ASD as a majority of the approaches used are linear and many individuals with ASD demonstrate discrepant profiles (e.g., exceptional memory in a nonverbal child). Profiles in the affected family members suggest that subgroups of individuals with ASD may exist who are high functioning in one area but who are low functioning in others, suggesting a dimensional approach to classifying ASDs rather than ASDs existing on a single, unitary severity gradient.

The unaffected family members' results also suggested subgroups. Their profiles, while not as uneven as the affected members, were differentiated based on

social abilities, suggesting that subclinically affected family members may exhibit profiles similar to affected individuals. When the profiles between the two groups were compared (average IQ), the average adaptive affected cluster appeared to be similar to the possible BAP unaffected cluster.

These results suggest two implications. First, subtypes of ASD may exist and may be best identified using a dimensional approach that considers constructs outside the diagnostic criteria. Second, unaffected family members may demonstrate similar profiles but at subclinical levels. Each of these implications is discussed in more detail.

Early research in the area of cluster analysis in autism suggested that individuals with pervasive developmental disorders fall into subgroups based on severity of impairment (Rescorla, 1988; Siegel, Anders, Ciaranello, Bienenstock, & Kraemer, 1986). However, much of this work was done before the introduction of DSM-IV-TR diagnostic criteria, which broadened the definition of autism (American Psychiatric Association, 2000). Thus, most individuals who met the diagnostic criteria for pervasive developmental disorder would have been more mildly affected than those who met the criteria for autism. However, three studies included a broader spectrum of functioning (Eaves, Ho, & Eaves, 1994; Prior et al., 1998; Waterhouse et al., 1996). For example, Waterhouse et al. compared IQ and behavior among individuals diagnosed with pervasive developmental disorder or autistic disorder and found that those with pervasive developmental disorder yielded higher VIQ, PIQ, and Vineland Scales of Adaptive Functioning scores

compared with those with autistic disorder, suggesting an overall severity gradient. Similarly, Eaves et al. found results that also suggested a severity gradient. In this study, individuals fell into clusters based on severity (e.g., IQ in the mentally handicapped range with behavior in the impaired range).

The present study differs from earlier work in several important ways. First, the present study focused solely on individuals with IQ scores above 70, whereas past research focused on lower-functioning individuals or mixed high- and low-IQ individuals, which may have made it difficult to identify profiles not driven primarily by IQ level. Thus, all participants in the current study were, by definition, high functioning, making it possible to identify subgroups within that IQ range. Second, the present study utilized a continuous measure of social ability (i.e., the Social Responsiveness Scale) rather than autism diagnostic classifications, which allowed subgroups to be formed separate from diagnostic categories. The four affected groups showed similar levels of social impairment, suggesting that symptom severity or a severity gradient was not driving the cluster membership. Finally, the current study examined multiple measures outside the diagnostic criteria, including language, IQ, adaptive functioning, and behavior. Earlier studies did not use such a wide range of constructs, which may have resulted in a cumulative effect of adding symptoms (e.g., finding that individuals with more symptoms or more severe symptoms also have more impaired intellectual functioning).

Ring, Woodbury-Smith, Watson, Wheelwright, and Baron-Cohen (2008) utilized a cluster analysis on high-functioning individuals with ASD, focusing solely on items from the autism spectrum quotient (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001). Four clusters were identified that suggested a severity gradient (e.g., mild to severe scores on the autism spectrum quotient). The authors suggested that this finding supported a unitary spectrum model of autism in which the heterogeneity observed in individuals was a result of a severity gradient rather than profiles that result in subtypes. However, the current study utilized only a measure of ASD symptoms and was unable to determine whether other factors such as IQ or age played a role. Thus, while the current study improved upon earlier studies that focused on lower-functioning individuals or that included both low- and high-functioning individuals, it did not examine variables outside the diagnostic criteria in which dimensional profiles might be found. In the current data, while Group 2 was clearly the lowest functioning in terms of cognitive and adaptive skills, they did not seem to have more severe autism symptoms. This finding suggests that social impairment may not be universally related to cognitive and adaptive impairments.

The current results are consistent with a recent study utilizing a more dimensional approach. Szatmari et al. (2002) utilized a factor analysis to study cognitive and adaptive features in ASD. Similar to the current results, they concluded that cognitive and adaptive measures were two separate factors or dimensions rather than on a continuum of severity with one another. They also

found that IQ was not correlated with symptom severity, which is similar to the current results.

Finally, the current results are consistent with a phenotype-genotype study of sibships. MacLean et al. (1999) found that neither pervasive developmental disorder diagnosis nor symptom severity ran together within families. In other words, within a particular sibship, a proband may have a different pervasive developmental disorder diagnosis and level of symptom severity than their affected sibling. Both their results and the results of the current study suggest that the mechanisms for level of functioning (i.e., IQ and adaptive behavior) may differ from those of pervasive developmental disorder symptom severity. In the current study, the unaffected family members' results shed further light on this possibility.

The current study is the first to examine profiles in family members. The two clusters identified in the unaffected family members suggest that some unaffected family members may demonstrate characteristics of the BAP and show IQ profiles similar to the highest-functioning individuals with ASD and that other family members are unaffected with no indication of the BAP and their own IQ profile. Previous studies have been able to identify BAP subgroups in families with ASD using the Social Responsiveness Scale and other measures of social functioning (Bailey et al., 1995; Bailey et al., 1998; Folstein & Rutter, 1977; Piven, Palmer, Jacobi et al., 1997; Szatmari, Jones et al., 1995; Szatmari et al., 1998) or examined IQ profiles in family members (Piven & Palmer, 1997; Piven, Palmer, Jacobi et al., 1997; Piven, Palmer, Landa et al., 1997) but not both.

Previous studies of IQ in relatives have yielded mixed results, with some finding higher VIQ scores in relatives (Fombonne et al., 1997) and others finding lower FSIQ and PIQ (Folstein et al., 1999). However, these studies have not been able to utilize measures of BAP in addition to IQ. Fombonne et al. identified a BAP group in their unaffected family members and found that IQ was generally lower compared with the unaffected family members. The current data did not find this difference between the BAP and unaffected group but did identify a larger discrepancy, although not clinically significant, in the BAP group in the direction of better PIQ scores. One other study attempted to look at social behavior and IQ in family members (Szatmari et al., 1996). They identified multiplex families with more than one member with an ASD and measured IQ, adaptive skills, and behavior in the affected individuals and IQ, adaptive behavior, and pervasive developmental disorder symptoms in the unaffected individuals. Results indicated that pervasive developmental disorder symptoms were not related to IQ. However, this study was conducted before continuous measures of social ability were available. Thus, the researchers classified probands, unaffected family members, and affected siblings into categories based on ADI and Autism Diagnostic Observation Schedule-Generic for the affected individuals and a family history interview for the unaffected siblings. It is possible that continuous measures of social ability would classify participants differently. Thus, further studies are needed to clarify the role of IQ, if any, in BAP subgroups of families with ASD.

With regard to language, several researchers have found that family members of those with ASD demonstrate language impairments similar to those with ASD (Piven, Palmer, Jacobi et al., 1997; Plumet et al., 1995; Wolk & Edwards, 1993). The current study examined language in terms of discrepancy scores (receptive–expressive) and found that the unaffected family members demonstrated a 12-point discrepancy in favor of receptive language compared with expressive and that the BAP group demonstrated evenly developed language abilities. This difference is likely not clinically meaningful; thus, it should be interpreted with caution. However, this difference does suggest that the specific role of language in unaffected family members needs further study.

The current results suggest that the highest-functioning group with ASD appeared to be similar to the BAP group in the unaffected relatives. Previous genetic research has suggested that relatives of high-functioning affected individuals may demonstrate BAP characteristics (Szatmari, 2000). Specifically, individuals diagnosed with high-functioning pervasive developmental disorder, as indicated by IQ or adaptive scores, were more likely to have relatives with BAP characteristics compared with individuals considered to have low-functioning pervasive developmental disorder. This finding suggests that the genotype associated with high-functioning pervasive developmental disorder, regardless of subtype, may be expressed in their relatives. In the current sample, many in Groups 1 and 4 were related to individuals within that same cluster, and most of the individuals in Group 4 were not related to individuals in clusters 2 and 3.

Limitations of the Present Study and Future Directions

One of the inherent limitations of this study was that an exploratory analysis was used to examine the data. Although cluster analysis was the best method for identifying potential profiles of individuals with multidimensional data, cluster analysis has limitations (Magnusson, 1995), and results should be interpreted with caution. Future studies are needed to validate the identified clusters as distinct subgroups in ASD. A variety of validation methods could be used, including factor analysis, to measure external variables and to compare different samples. Additional statistical models could also be helpful such as Q-factor analysis, which is a form of factor analysis that clusters individuals rather than variables.

In addition, interpretations regarding the measures of language used should be cautioned. In the current study, the language variable was based on multiple measures (i.e., Clinical Evaluation of Language Fundamentals, VIQ, and Expanded Token Test), which may not measure similar constructs. Since mixed measures were used to yield discrepancy scores (expressive-receptive), it may be that the discrepancy score VIQ-Expanded Token Test was not qualitatively similar to the Clinical Evaluation of Language Fundamentals discrepancy score (expressive-receptive). The expressive domain of the Clinical Evaluation of Language Fundamentals was correlated with the VIQ as was the receptive domain. The Expanded Token Test was correlated with both VIQ and PIQ, possibly suggesting that it measured more than receptive language abilities. Thus, it may be that the Expanded Token Test did not adequately represent the construct of receptive

language. Differences related to language were not identified; however, it still may be possible that language plays an important role in classifying ASDs.

Another important factor not examined in the current study was family membership. As ASDs are thought to have a genetic etiology, it is likely that family membership could have played an important but complex role in the current study. The current study was not able to thoroughly examine this role, but future studies may.

Another limitation of the present study was that longitudinal data are needed to determine whether the profiles viewed here are static or may change with age. The current study would be considered cross-sectional, which may pose problems for classifying ASDs (Szatmari, 2000). Longitudinal samples this large are not currently available.

An additional limitation is that adaptive-functioning and maladaptive-behavior measures were not available for the unaffected family members for comparison of results. There is a general lack of continuous measures (from the impaired to the normal or above-average range) available for this type of research. At the beginning of this study, only two such measures of social ability were available. At the time of this writing, an additional measure of the BAP has become available (Hurley, Losh, Parlier, Reznick, & Piven, 2007) as has an adult and child version of pragmatic language (Botting, 2004). However, additional measures of skills that might be associated with ASD but not part of the diagnostic criteria are needed.

Other factors should also be examined. For example, it has been shown that IQ and adaptive-functioning scores can be influenced by intervention and treatment in ASD. However, my limited understanding of the essential ingredients of intervention (e.g., onset, intensity, and duration) and the lack of uniformly available treatment make it impossible to fully understand the relationship between intervention and ability profiles. As opportunities for intervention increase for children with ASD, there may come a time when intervention variables can be more fully operationalized.

Alternative Interpretations

An important alternative interpretation to these results may exist. First, because participants were administered the appropriate test type for IQ and language based on age, some of these findings may be due to the variety of tests administered. In other words, it may be that clusters were influenced by the type of test given. Post hoc analyses examined these variables categorically and found that clusters 1 and 3 differed in the affected group; however, this may be only one indication of how test type may have affected cluster membership. The best way to determine the effects of test type would be to select participants in a single age range who all received the same test or to test the same individuals over time as they grow from one age to another and, thus, from one test to another.

CONCLUSION

The present study used cluster analysis to examine the cognitive and behavioral profiles of families with ASD. Four clusters emerged in the affected family members and two clusters emerged in the unaffected family members. The identified profiles suggest that multiple subtypes of ASD may exist, each with their own distinct developmental profile, although longitudinal data are needed to confirm this. This is in contrast to research that suggests a unitary severity gradient of ASDs but is consistent with research that suggests utilizing a dimensional approach to subtyping ASDs. Results also suggest that subclinical forms of ASDs may be present in family members for those with a diagnosable ASD and that these individuals may demonstrate cognitive and social profiles similar to the highest functioning affected group. These results may also suggest that (a) cognitive and behavioral constructs are potentially useful for subtyping and identifying subclinical forms of ASDs and (b) the subclinical forms of ASDs may shed light on potential genetic etiologies.

REFERENCES

Akshoomoff, N. (2006). Use of the Mullen Scales of Early Learning for the assessment of young children with autism spectrum disorders. *Child Neuropsychology, 12*(4-5), 269-277.

Aman, M., & Singh, N. (1986). *The Aberrant Behavior Checklist.* East Aurora, NY: Slosson Educational Publications, Inc.

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: Author.

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text rev.). Washington, DC: Author.

Amir, R. E., Van den Veyver, I. B., Wan, M., Tran, C. Q., Francke, U., & Zoghbi, H. Y. (1999). Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. *Nature and Genetics, 23*(2), 185-188.

Asperger, H. (1944). Autistic psychopathy. *Archiv fuer Psychiatrie und Nervenkra.*

Axelrod, B. N. (2002). Validity of the Wechsler Abbreviated Scale of Intelligence and other very short forms of estimating intellectual functioning. *Assessment, 9*(1), 17-23.

Bailey, A., Le Couteur, A., Gottesman, I., Bolton, P., Simonoff, E., Yuzda, E. et al. (1995). Autism as a strongly genetic disorder: Evidence from a British twin study. *Psychological Medicine, 25*(1), 63-77.

Bailey, A., Luthert, P., Dean, A., Harding, B., Janota, I., Montgomery, M. et al. (1998). A clinicopathological study of autism. *Brain, 121,* 889-905.

Barnhill, G., Hagiwara, T., Myles, B. S., & Simpson, R. L. (2000). Asperger syndrome: A study of the cognitive profiles of 37 children and adolescents. *Focus on Autism and Other Developmental Disabilities, 15*(3), 146-153.

Baron-Cohen, S., Wheelwright, S., Skinner, R., Martin, J., & Clubley, E. (2001). The autism-spectrum quotient (AQ): Evidence from Asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. *Journal of Autism and Developmental Disorders, 31*(1), 5-17.

Bennett, T., Szatmari, P., Bryson, S., Volden, J., Zwaigenbaum, L., Vaccarella, L. et al. (2008). Differentiating autism and Asperger syndrome on the basis of language delay or impairment. *Journal of Autism and Developmental Disorders, 38*(4), 616-625.

Billstedt, E., Gillberg, C., & Gillberg, C. (2005). Autism after adolescence: Population-based 13- to 22-year follow-up study of 120 individuals with autism diagnosed in childhood. *Journal of Autism and Developmental Disorders, 35*(3), 351-360.

Botting, N. (2004). Children's Communication Checklist (CCC) scores in 11-year-old children with communication impairments. *International Journal of Language and Communication Disorders, 39*(2), 215-227.

Boutin, P., Maziade, M., Merette, C., Mondor, M., Bedard, C., & Thivierge, J. (1997). Family history of cognitive disabilities in first-degree relatives of autistic and mentally retarded children. *Journal of Autism and Developmental Disorders, 27*(2), 165-176.

Bradford, Y. (2001). Incorporating language phenotypes strengthens evidence of linkage to autism. *American Journal of Medical Genetics, 105*(8), 539-547.

Brooks, B. L., & Weaver, L. E. (2005). Concurrent validity of WAIS-III short forms in a geriatric sample with suspected dementia: Verbal, performance, and full scale IQ scores. *Archives of Clinical Neuropsychology, 20*(8), 1043-1051.

Buitelaar, J. K., Van der Gaag, R., Klin, A., & Volkmar, F. (1999). Exploring the boundaries of pervasive developmental disorder not otherwise specified: Analyses of data from the DSM-IV autistic disorder field trial. *Journal of Autism and Developmental Disorders, 29*(1), 33-43.

Burd, L., Ivey, M., Barth, A., & Kerbeshian, J. (1998). Two males with childhood disintegrative disorder: A prospective 14-year outcome study. *Developmental Medicine Child Neurology, 40*(10), 702-707.

Buxbaum, J. D., Silverman, J. M., Smith, C. J., Kilifarski, M., Reichert, J., Hollander, E. et al. (2001). Evidence for a susceptibility gene for autism on chromosome 2 and for genetic heterogeneity. *American Journal of Medical Genetics, 68*(6), 1514-1520.

Cantor, R. M., Kono, N., Duvall, J. A., Alvarez-Retuerto, A., Stone, J. L., Alarcon, M. et al. (2005). Replication of autism linkage: Fine-mapping peak at 17q21. *American Journal of Human Genetics, 76*(6), 1050-1056.

Carter, A. S., Black, D. O., Tewani, S., Connolly, C. E., Kadlec, M. B., & Tager-Flusberg, H. (2007). Sex differences in toddlers with autism spectrum disorders. *Journal of Autism and Developmental Disorders, 37*(1), 86-97.

Chakrabarti, S., & Fombonne, E. (2001). Pervasive developmental disorders in preschool children. *Journal of the American Medical Association, 285*(24), 3093-3099.

Comrey, A. L. (1985). A method for removing outliers to improve factor analytic results. *Multivariate Behavioral Research, 20,* 273-281.

Condouris, K., Meyer, E., & Tager-Flusberg, H. (2003). The relationship between standardized measures of language and measures of spontaneous speech in children with autism. *American Journal of Speech Language Pathology, 12*(3), 349-358.

Constantino, J. N. (2002). *The Social Responsiveness Scale.* Los Angeles: Western Psychological Services.

Constantino, J. N., & Todd, R. D. (2003). Autistic traits in the general population: A twin study. *Archives of General Psychiatry, 60*(5), 524-530.

Coon, H., Dunn, D., Lainhart, J., Miller, J., Hamil, C., Battaglia, A. et al. (2005). Possible association between autism and variants in the brain-expressed tryptophan hydroxylase gene (TPH2). *American Journal of Medical Genetics B Neuropsychiatric Genetics, 135*(1), 42-46.

Dawson, G., Estes, A., Munson, J., Schellenberg, G., Bernier, R., & Abbott, R. (2007). Quantitative assessment of autism symptom-related traits in probands and parents: Broader Phenotype Autism Symptom Scale. *Journal of Autism and Developmental Disorders, 37*(3), 523-536.

Dawson, G., Webb, S., Schellenberg, G. D., Dager, S., Friedman, S., Aylward, E. et al. (2002). Defining the broader phenotype of autism: Genetic, brain, and behavioral perspectives. *Developmental Psychopathology, 14*(3), 581-611.

De Bellis, M. D., Keshavan, M. S., Beers, S. R., Hall, J., Frustaci, K., Masalehdan, A. et al. (2001). Sex differences in brain maturation during childhood and adolescence. *Cerebral Cortex, 11*(6), 552-557.

De Renzi, E., & Faglioni, P. (1978). Normative data and screening power of a shortened version of the Token Test. *Cortex, 14*(1), 41-49.

Dicerbo, K. E., & Barona, A. (2001). A convergent validity study of the differential ability scales and the Wechsler Intelligence Scale for Children—Third Edition with Hispanic children. *Journal of Psychoeducational Assessment, 18*(4), 344-352.

Dumont, R., Cruse, C. L., Price, L., & Whelley, P. (1996). The relationship between the DAS and the WISC-III for students with learning disabilities. *Psychology in the Schools, 33*(3), 203-209.

Eaves, L. C., Ho, H. H., & Eaves, D. M. (1994). Subtypes of autism by cluster analysis. *Journal of Autism and Developmental Disorders, 24*(1), 3-22.

Eisenmajer, R., Prior, M., Leekam, S., Wing, L., Gould, J., Welham, M. et al. (1996). Comparison of clinical symptoms in autism and Asperger disorder. *Journal of the American Academy of Child and Adolescent Psychiatry, 35*(11), 1523-1531.

Elliott, C. (1990). *Differential Abilities Scale.* San Antonio, TX: The Psychological Corporation.

Fisher, L., & Ransom, D. C. (1995). An empirically derived typology of families: I. Relationships with adult health. *Family Process Journal, 34*(2), 161-182.

Folstein, S. E., & Rutter, M. (1977). Genetic influences and infantile autism. *Nature, 265*(5596), 726-728.

Folstein, S. E., Santangelo, S. L., Gilman, S. E., Piven, J., Landa, R., Lainhart, J. et al. (1999). Predictors of cognitive test patterns in autism families. *Journal of Child Psychology and Psychiatry, 40*(7), 1117-1128.

Fombonne, E. (1999). The epidemiology of autism: A review. *Psychology and Medicine, 29*(4), 769-786.

Fombonne, E. (2003). The prevalence of autism. *Journal of the American Medical Association, 289*(1), 87-89.

Fombonne, E., Bolton, P., Prior, J., Jordan, H., & Rutter, M. (1997). A family study of autism: Cognitive patterns and levels in parents and siblings. *Journal of Child Psychology and Psychiatry, 38*(6), 667-683.

Giedd, J. N., Blumenthal, J., Jeffries, N. O., Castellanos, F. X., Liu, H., Zijdenbos, A. et al. (1999). Brain development during childhood and adolescence: A longitudinal MRI study. *Nature and Neuroscience, 2*(10), 861-863.

Gillberg, C. (1987). Autistic symptoms in Rett syndrome: The first two years according to mother reports. *Brain Development, 9*(5), 499-501.

Hagberg, B. A. (1989). Rett syndrome: Clinical peculiarities, diagnostic approach, and possible cause. *Pediatric Neurology, 5*(2), 75-83.

Hagberg, B. A., Aicardi, J., Dias, K., & Ramos, O. (1983). A progressive syndrome of autism, dementia, ataxia, and loss of purposeful hand use in girls. Rett's syndrome: Report of 35 cases. *Annals of Neurology, 14*(4), 471-479.

Hair, J. F., Anderson, R. E., Tatham, R. L., & Black, W. C. (1998). *Multivariate data analysis* (5th ed.). Upper Saddle River, NJ: Prentice Hall.

Hampson, E. (1995). Spatial cognition in humans: Possible modulation by androgens and estrogens. *Journal of Psychiatry Neuroscience, 20*(5), 397-404.

Henry, D. B., Tolan, P. H., & Gorman-Smith, D. (2005). Cluster analysis in family psychology research. *Journal of Family Psychology, 19*(1), 121-132.

Herbert, M. R., Harris, G. J., Adrien, K. T., Ziegler, D. A., Makris, N., Kennedy, D. N. et al. (2002). Abnormal asymmetry in language association cortex in autism. *Annals of Neurology, 52*(5), 588-596.

Hoshino, Y., Kaneko, M., Yashima, Y., Kumashiro, H., Volkmar, F. R., & Cohen, D. J. (1987). Clinical features of autistic children with setback course in their infancy. *Japanese Journal of Psychiatry and Neurology, 41*(2), 237-245.

Howlin, P. (2003). Outcome in high-functioning adults with autism with and without early language delays: Implications for the differentiation between autism and Asperger syndrome. *Journal of Autism and Developmental Disorders, 33*(1), 3-13.

Hurley, R. S., Losh, M., Parlier, M., Reznick, J. S., & Piven, J. (2007). The Broad Autism Phenotype Questionnaire. *Journal of Autism and Developmental Disorders, 37*(9), 1679-1690.

Jansiewicz, E. M., Goldberg, M. C., Newschaffer, C. J., Denckla, M. B., Landa, R., & Mostofsky, S. H. (2006). Motor signs distinguish children with high functioning autism and Asperger syndrome from controls. *Journal of Autism and Developmental Disorders, 36*(5), 613-621.

Jones, J. J., van Schaik, P., & Witts, P. (2006). A factor analysis of the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) in a low IQ sample. *British Journal of Clinical Psychology, 45*(2), 145-152.

Joseph, R. M., Tager-Flusberg, H., & Lord, C. (2002). Cognitive profiles and social-communicative functioning in children with autism spectrum disorder. *Journal of Child Psychology and Psychiatry, 43*(6), 807-821.

Kanner, L. (1943). Autistic disturbances of affective conduct. *Nervous Child, 2,* 217-250.

Kanner, L., & Eisenberg, L. (1956). Child psychiatry; mental deficiency. *American Journal of Psychiatry, 112*(7), 531-534.

Kimura, D. (1992). Sex differences in the brain. *Scientific American, 9*(267), 80-87.

Kjelgaard, M. M., & Tager-Flusberg, H. (2001). An investigation of language impairment in autism: Implications for genetic subgroups. *Language Cognitive Process, 16*(2-3), 287-308.

Klin, A., Volkmar, F. R., Sparrow, S. S., Cicchetti, D. V., & Rourke, B. P. (1995). Validity and neuropsychological characterization of Asperger syndrome: Convergence with nonverbal learning disabilities syndrome. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 36*(7), 1127-1140.

Koyama, T., Tachimori, H., Osada, H., & Kurita, H. (2006). Cognitive and symptom profiles in high-functioning pervasive developmental disorder not otherwise specified and attention-deficit/hyperactivity disorder. *Journal of Autism and Developmental Disorders, 36*(3), 373-380.

Koyama, T., Tachimori, H., Osada, H., Takeda, T., & Kurita, H. (2007). Cognitive and symptom profiles in Asperger syndrome and high-functioning autism. *Psychiatry and Clinical Neuroscience, 61*(1), 99-104.

Kurita, H. (1985). Infantile autism with speech loss before the age of thirty months. *Journal of the American Academy of Child Psychiatry, 24*(2), 191-196.

Kurita, H., Koyama, T., Setoya, Y., Shimizu, K., & Osada, H. (2004). Validity of childhood disintegrative disorder apart from autistic disorder with speech loss. *European Child and Adolescent Psychiatry Journal, 13*(4), 221-226.

Landa, R., & Garrett-Mayer, E. (2006). Development in infants with autism spectrum disorders: A prospective study. *Journal of Child Psychology and Psychiatry, 47*(6), 629-638.

Lincoln, A. J., Courchesne, E., Allen, M., Hansen, E., & Ene, M. (1998). *Neurobiology of Asperger syndrome: Seven case studies and quantitative magnetic resonance imaging.* New York: Plenum.

Lockyer, L., & Rutter, M. (1969). A five- to fifteen-year follow-up study of infantile psychosis. *British Journal of Psychiatry, 115,* 865–882.

Lord, C., & Paul, R. (1997). Language and communication in autism. In D. J. Cohen & F. R. Volkmar (Eds.), *Handbook of autism and pervasive developmental disorders* (pp. 195-225). New York: Wiley.

Lord, C., Risi, S., Lambrecht, L., Cook, E. H., Jr., Leventhal, B. L., DiLavore, P. C. et al. (2000). The Autism Diagnostic Observation Schedule-Generic: A standard measure of social and communication deficits associated with the spectrum of autism. *Journal of Autism and Developmental Disorders, 30*(3), 205-223.

Lord, C., Rutter, M., & Le Couteur, A. (1994). Autism Diagnostic Interview-Revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *Journal of Autism and Developmental Disorders, 24*(5), 659-685.

Lotspeich, L. J., Kwon, H., Schumann, C. M., Fryer, S. L., Goodlin-Jones, B. L., Buonocore, M. H. et al. (2004). Investigation of neuroanatomical differences between autism and Asperger syndrome. *Archives of General Psychiatry, 61*(3), 291-298.

MacLean, J. E., Szatmari, P., Jones, M. B., Bryson, S. E., Mahoney, W. J., Bartolucci, G. et al. (1999). Familial factors influence level of functioning in pervasive developmental disorder. *Journal of the American Academy of Child and Adolescent Psychiatry, 38*(6), 746-753.

Magnusson, D. (1995). *Individual development: A holistic integrated model. Reports from the Department of Psychology, Stockholm University* (No. 796). Stockholm, Sweden: Department of Psychology, Stockholm University.

Manjiviona, J., & Prior, M. (1999). Neuropsychological profiles of children: Asperger syndrome and autism. *Autism, 3,* 327-356.

Mawhood, L., Howlin, P., & Rutter, M. (2000). Autism and developmental receptive language disorder—a comparative follow-up in early adult life. I: Cognitive and language outcomes. *Journal of Child Psychology and Psychiatry, 41*(5), 547-559.

Mayes, S. D., & Calhoun, S. L. (2003). Analysis of WISC-III, Stanford-Binet: IV, and academic achievement test scores in children with autism. *Journal of Autism and Developmental Disorders, 33*(3), 329-341.

Mayes, S. D., & Calhoun, S. L. (2004). Similarities and differences in Wechsler Intelligence Scale for Children—Third Edition (WISC-III) profiles: Support for subtest analysis in clinical referrals. *Clinical Neuropsychology, 18*(4), 559-572.

McLennan, J. D., Lord, C., & Schopler, E. (1993). Sex differences in higher functioning people with autism. *Journal of Autism and Developmental Disorders, 23*(2), 217-227.

Miller, J. N., & Ozonoff, S. (1997). Did Asperger cases have Asperger disorder? A research note. *Journal of Child Psychology and Psychiatry, 38*(2), 247-251.

Miller, J. N., & Ozonoff, S. (2000). The external validity of Asperger disorder: Lack of evidence from the domain of neuropsychology. *Journal of Abnormal Psychology, 109*(2), 227-238.

Milligan, G. W. (1980). An examination of the effect of six types of error perturbation of fifteen clustering algorithms. *Psychometrika, 45,* 325-342.

Minshew, N. J., Turner, C. A., & Goldstein, G. (2005). The application of short forms of the Wechsler Intelligence Scale in adults and children with high functioning autism. *Journal of Autism and Developmental Disorders, 35*(1), 45-52.

Morgan, B. T., & Ray, A. P. G. (1995). Nonuniqueness and inversion in cluster analysis. *Applied Statistics, 44,* 117-134.

Morice, R., & McNicol, D. (1985). The comprehension and production of complex syntax in schizophrenia. *Cortex, 21*(4), 567-580.

Mouridsen, S. E., Rich, B., & Isager, T. (1998). Validity of childhood disintegrative psychosis: General findings of a long-term follow-up study. *British Journal of Psychiatry, 172,* 263-267.

Mullen, E. (1995). *Mullen Scales of Early Learning.* Circle Pines, MN: American Guidance Service.

Newbury, D. F., Bonora, E., Lamb, J. A., Fisher, S. E., Lai, C. S., Baird, G. et al. (2002). FOXP2 is not a major susceptibility gene for autism or specific language impairment. *American Journal of Human Genetics, 70*(5), 1318-1327.

Ozonoff, S., South, M., & Miller, J. (2000). DSM-IV-defined Asperger disorder: Cognitive, behavioral, and early history differentiation from high functioning autism. *Autism, 4,* 29-46.

Perez, E., Slate, J. R., Neeley, R., McDaniel, M., Baggs, T., & Layton, K. (1995). Validity of the CELF-R, TONI and sit for children referred for auditory processing problems. *Journal of Clinical Psychology, 51,* 540-543.

Pickles, A., Bolton, P., Macdonald, H., Bailey, A., Le Couteur, A., Sim, C. H. et al. (1995). Latent-class analysis of recurrence risks for complex phenotypes with selection and measurement error: A twin and family history study of autism. *American Journal of Human Genetics, 57*(3), 717-726.

Pilowsky, T., Yirmiya, N., Shalev, R. S., & Gross-Tsur, V. (2003). Language abilities of siblings of children with autism. *Journal of Child Psychology and Psychiatry, 44*(6), 914-925.

Piven, J., & Palmer, P. (1997). Cognitive deficits in parents from multiple-incidence autism families. *Journal of Child Psychology and Psychiatry, 38*(8), 1011-1021.

Piven, J., Palmer, P., Jacobi, D., Childress, D., & Arndt, S. (1997). Broader autism phenotype: Evidence from a family history study of multiple-incidence autism families. *American Journal of Psychiatry, 154*(2), 185-190.

Piven, J., Palmer, P., Landa, R., Santangelo, S., Jacobi, D., & Childress, D. (1997). Personality and language characteristics in parents from multiple-incidence autism families. *American Journal of Medical Genetics, 74*(4), 398-411.

Plumet, M. H., Goldblum, M. C., & Leboyer, M. (1995). Verbal skills in relatives of autistic females. *Cortex, 31*(4), 723-733.

Prior, M., Eisenmajer, R., Leekam, S., Wing, L., Gould, J., Ong, B. et al. (1998). Are there subgroups within the autistic spectrum? A cluster analysis of a group of children with autistic spectrum disorders. *Journal of Child Psychology and Psychiatry, 39*(6), 893-902.

Rapin, I. (1996). Practitioner review: Developmental language disorders. A clinical update. *Journal of Child Psychology and Psychiatry, 37*(6), 643-655.

Rapin, I., & Dunn, M. (2003). Update on the language disorders of individuals on the autistic spectrum. *Brain Development, 25*(3), 166-172.

Rescorla, L. (1988). Cluster analytic identification of autistic preschoolers. *Journal of Autism and Developmental Disorders, 18*(4), 475-492.

Ring, H., Woodbury-Smith, M., Watson, P., Wheelwright, S., & Baron-Cohen, S. (2008). Clinical heterogeneity among people with high functioning autism spectrum conditions: Evidence favoring a continuous severity gradient. *Behavior and Brain Function, 4,* 11.

Ringe, W. K., Saine, K. C., Lacritz, L. H., Hynan, L. S., & Cullum, C. M. (2002). Dyadic short forms of the Wechsler Adult Intelligence Scale-III. *Assessment, 9*(3), 254-260.

Risch, N., Spiker, D., Lotspeich, L., Nouri, N., Hinds, D., Hallmayer, J. et al. (1999). A genomic screen of autism: Evidence for a multilocus etiology. *American Journal of Human Genetics, 65*(2), 493-507.

Ritvo, E. R., & Ariella Ritvo, A. (2006). Are the majority of children with autism mentally retarded? *Focus on Autism and Other Developmental Disabilities, 21*(2), 84-85.

Ritvo, E. R., Ritvo, R., Freeman, B. J., & Mason-Brothers, A. (1994). Clinical characteristics of mild autism in adults. *Comprehensive Psychiatry, 35*(2), 149-156.

Rogers, S. J., & DiLalla, D. L. (1990). Age of symptom onset in young children with pervasive developmental disorders. *Journal of the American Academy of Child and Adolescent Psychiatry, 29*(6), 863-872.

Rumsey, J. M. (1992). Neuropsychological studies of high-level autism. In E. Schopler & G. Mesibov (Eds.), *High-functioning individuals with autism* (pp. 41-64). New York: Plenum Press.

Saklofske, D. H., Hildebrand, D. K., & Gorsuch, R. L. (2000). Replication of the factor structure of the Wechsler Adult Intelligence Scale-Third Edition with a Canadian sample. *Psychological Assessment, 12*(4), 436-439.

Segawa, M., & Nomura, Y. (2005). Rett syndrome. *Current Opinion in Neurology, 18*(2), 97-104.

Shao, Y., Raiford, K. L., Wolpert, C. M., Cope, H. A., Ravan, S. A., Ashley-Koch, A. A. et al. (2002). Phenotypic homogeneity provides increased support for linkage on chromosome 2 in autistic disorder. *American Journal of Medical Genetics, 70*(4), 1058-1061.

Siegel, B., Anders, T. F., Ciaranello, R. D., Bienenstock, B., & Kraemer, H. C. (1986). Empirically derived subclassification of the autistic syndrome. *Journal of Autism and Developmental Disorders, 16*(3), 275-293.

Siegel, D. J., Minshew, N. J., & Goldstein, G. (1996). Wechsler IQ profiles in diagnosis of high-functioning autism. *Journal of Autism and Developmental Disorders, 26*(4), 389-406.

Silverman, J. M., Smith, C. J., Schmeidler, J., Hollander, E., Lawlor, B. A., Fitzgerald, M. et al. (2002). Symptom domains in autism and related conditions: Evidence for familiality. *American Journal of Medical Genetics, 114*(1), 64-73.

Smalley, S. L., & Collins, F. (1996). Brief report: Genetic, prenatal, and immunologic factors. *Journal of Autism and Developmental Disorders, 26*(2), 195-198.

Sneath, P. H., & Sokal, R. R. (1973). *Numerical taxonomy.* San Francisco: Freeman.

South, M., Ozonoff, S., & McMahon, W. M. (2005). Repetitive behavior profiles in Asperger syndrome and high-functioning autism. *Journal of Autism and Developmental Disorders, 35*(2), 145-158.

Sparrow, S., Balla, D., & Cicchetti, D. (1984). *The Vineland Adaptive Behavior Scales.* Bloomington, MN: American Guidance Service.

Spek, A. A., Scholte, E. M., & van Berckelaer-Onnes, I. A. (2008). Brief report: The use of WAIS-III in adults with HFA and Asperger syndrome. *Journal of Autism and Developmental Disorders, 38*(4), 782-787.

Spence, S. J., Cantor, R. M., Chung, L., Kim, S., Geschwind, D. H., & Alarcon, M. (2006). Stratification based on language-related endophenotypes in autism: Attempt to replicate reported linkage. *American Journal of Medical Genetics B Neuropsychiatric Genetics, 141B*(6), 591-598.

SPSS, Inc. (2006). *SPSS base 15.0 for Windows user's guide.* Chicago: Author.

Steffenburg, S., Gillberg, C., Hellgren, L., Andersson, L., Gillberg, I. C., Jakobsson, G. et al. (1989). A twin study of autism in Denmark, Finland, Iceland, Norway, and Sweden. *Journal of Child Psychology and Psychiatry, 30*(3), 405-416.

Stone, J. L., Merriman, B., Cantor, R. M., Yonan, A. L., Gilliam, T. C., Geschwind, D. H. et al. (2004). Evidence for sex-specific risk alleles in autism spectrum disorder. *American Journal of Human Genetics, 75*(6), 1117-1123.

Szatmari, P. (2000). The classification of autism, Asperger syndrome, and pervasive developmental disorder. *Canadian Journal of Psychiatry, 45*(8), 731-738.

Szatmari, P., Archer, L., Fisman, S., Streiner, D. L., & Wilson, F. (1995). Asperger syndrome and autism: Differences in behavior, cognition, and adaptive functioning. *Journal of the American Academy of Child and Adolescent Psychiatry, 34*(12), 1662-1671.

Szatmari, P., Bryson, S. E., Boyle, M. H., Streiner, D. L., & Duku, E. (2003). Predictors of outcome among high functioning children with autism and Asperger syndrome. *Journal of Child Psychology and Psychiatry, 44*(4), 520-528.

Szatmari, P., Jones, M. B., Fisman, S., Tuff, L., Bartolucci, G., Mahoney, W. J. et al. (1995). Parents and collateral relatives of children with pervasive developmental disorders: A family history study. *American Journal of Medical Genetics, 60*(4), 282-289.

Szatmari, P., Jones, M. B., Holden, J., Bryson, S., Mahoney, W., Tuff, L. et al. (1996). High phenotypic correlations among siblings with autism and pervasive developmental disorders. *American Journal of Medical Genetics, 67*(4), 354-360.

Szatmari, P., Jones, M. B., Zwaigenbaum, L., & MacLean, J. E. (1998). Genetics of autism: Overview and new directions. *Journal of Autism and Developmental Disorders, 28*(5), 351-368.

Szatmari, P., Merette, C., Bryson, S. E., Thivierge, J., Roy, M. A., Cayer, M. et al. (2002). Quantifying dimensions in autism: A factor-analytic study. *Journal of the American Academy of Child and Adolescent Psychiatry, 41*(4), 467-474.

Tager-Flusberg, H. (2004). Do autism and specific language impairment represent overlapping language disorders? In M. Rice & S. Warren (Eds.), *Developmental language disorders: From phenotypes to etiologies* (pp. 31-52). New York: Erlbaum.

Tager-Flusberg, H., & Joseph, R. M. (2003). Identifying neurocognitive phenotypes in autism. *Philosophical Transactions of the Royal Society B: Biological Sciences, 358*(1430), 303-314.

Thompson, P. M., Giedd, J. N., Woods, R. P., MacDonald, D., Evans, A. C., & Toga, A. W. (2000). Growth patterns in the developing brain detected by using continuum mechanical tensor maps. *Nature, 404*(6774), 190-193.

Tsai, L. Y. (1992a). Diagnostic issues in high-functioning autism. In E. Schopler & G. Mesibov (Eds.), *High-functioning individuals with autism* (pp. 10-40). New York: Plenum Press.

Tsai, L. Y. (1992b). Is Rett syndrome a subtype of pervasive developmental disorders? *Journal of Autism and Developmental Disorders, 22*(4), 551-561.

Verte, S., Geurts, H. M., Roeyers, H., Oosterlaan, J., & Sergeant, J. A. (2006). Executive functioning in children with an autism spectrum disorder: Can we differentiate within the spectrum? *Journal of Autism and Developmental Disorders, 36*(3), 351-372.

Volkmar, F. R. (1992). Childhood disintegrative disorder: Issues for DSM-IV. *Journal of Autism and Developmental Disorders, 22*(4), 625-642.

Waller, N. G., Kaiser, H. A., Illian, J. B., & Manry, M. Y. (1998). A comparison of the classification capabilities of the 1-dimensional Kohonen Neural Network with two partitioning and three hierarchical cluster analysis algorithms. *Psychometrika, 63,* 5-22.

Ward, J. H. (1963). Hierarchical grouping to optimize an objective function. *Journal of the American Statistical Association, 58,* 236-244.

Wassink, T. H., Brzustowicz, L. M., Bartlett, C. W., & Szatmari, P. (2004). The search for autism disease genes. *Mental Retardation and Developmental Disabilities Research Review, 10*(4), 272-283.

Wassink, T. H., & Piven, J. (2000). The molecular genetics of autism. *Current Psychiatry Reports, 2*(2), 170-175.

Waterhouse, L., Morris, R., & Allen, D. A. (1996). Diagnosis and classification in autism. *Journal of Autism and Developmental Disorders, 26*(1), 59-86.

Wechsler, D. (1991). *Wechsler Intelligence Scale for Children-III.* San Antonio, TX: Harcourt Brace Jovanovich.

Wechsler, D. (1997). *Manual for the Wechsler Adult Intelligence Scale* (3rd ed.). San Antonio, TX: The Psychological Corporation.

Wechsler, D. (1999). *Wechsler Abbreviated Scale of Intelligence (WASI).* San Antonio, TX: The Psychological Corporation.

Wiig, E. H., Secord, W., & Semel, E. (1992). *Clinical Evaluation of Language Fundamentals-Preschool.* San Antonio, TX: The Psychological Corporation.

Wolk, L., & Edwards, M. L. (1993). The emerging phonological system of an autistic child. *Journal of Communication Disorders, 26*(3), 161-177.

Wymer, J. H., Rayls, K., & Wagner, M. T. (2003). Utility of a clinically derived abbreviated form of the WAIS-III. *Archives of Clinical Neuropsychology, 18*(8), 917-927.